A Dissertation on

A COMPREHENSIVE STUDY OF CARCINOMA TONGUE

Dissertation Submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the regulations for the award of the degree of

M.S. GENERAL SURGERY

BRANCH – I

GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU.

APRIL - 2013

CERTIFICATE

This is to certify that the dissertation entitled **"A COMPREHENSIVE STUDY OF CARCINOMA TONGUE"** is a genuine work done by **Dr.K.RAMAMOORTHI** for the partial fulfillment of the requirements for **M.S. Branch – I (General Surgery)** Examination of the Tamilnadu Dr.M.G.R. Medical University to be held in APRIL 2013. Under my supervision and the guidance of **Prof.Dr.S.VISWANATHAN, M.S.,** Department of General Surgery, Government Stanley Medical College and Hospital.

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DECLARATION

I, **Dr. K.RAMAMOORTHI,** solemnly declare that dissertation entitled, **"A COMPREHENSIVE STUDY OF CARCINOMA TONGUE"** is a bonafide work done by me in the Department of General Surgery at Govt.Stanley Medical College & Hospital, Chennai, under the guidance of. **Prof. S. .VISWANATHAN, M.S.,** Additional Professor of Surgery, unit Chief, Government Stanley Medical College and Hospital, Chennai-600 001.

The dissertation is submitted to Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the University regulations for the award of **M.S. Degree (Branch – I) in General Surgery** examination to be held in April 2013.

Place : Chennai.

Date :

(Dr.K.RAMAMOORTHI)

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yes	yes	yes	yes	yes	4	no	no	no	no	no	yes	yes

GASTROINTESTINAL STROMAL TUMOR: A RETROSPECTIVE STUDY

Dissertation
Submitted in partial fulfilment of the regulation of

M.S. DEGREE EXAMINATION
BRANCH I GENERAL SURGERY

Department of General Surgery
STANLEY MEDICAL COLLEGE AND HOSPITAL
CHENNAI – 600001

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY
CHENNAI

APRIL - 2013

CERTIFICATE

This is to certify that this dissertation is titled

"*GASTROINTESTINAL STROMAL TUMOR: A RETROSPECTIVE STUDY*"

is the bonafide work done by **Dr. SENDHIL RAJAN,** Post Graduate Student (2010 – 2013) in the Department of General Surgery, Stanley Medical College and Hospital, Chennai under the direct guidance and supervision and in partial fulfilment of the regulations laid down by the Tamil Nadu Dr. M.G.R. Medical University, Chennai for M.S. Branch I, General Surgery Degree Examination.

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DECLARATION

I, **Dr. SENDHIL RAJAN,** solemnly declare that the dissertation titled

"GASTROINTESTINAL STROMAL TUMOR: A RETROSPECTIVE STUDY"

is a bonafide work done by me at Govt. Stanley Medical College and Hospital from May 2010 to Oct 2012 under the guidance and supervision of my unit chief,

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This dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University towards the partial fulfilment of the requirements of M.S. Branch I, General Surgery degree examination.

PLACE: CHENNAI **Dr. SENDHIL RAJAN**

DATE:

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

GIST	Gastrointestinal Stromal Tumor
GI (as in GI tract)	Gastro Intestinal
CD (as in CD117)	Cluster of differentiation molecule
GANT	Gastrointestinal Autonomic Nerve Tumors
PDGFRA	Platelet-derived growth factor receptor, alpha polypeptide
ICC	Interstitial cells of Cajal
IHC	Immunohistochemistry
^{18}FDG	18-Fluorodeoxyglucose
PET	Positron Emission Tomography
HPF	High Power Field
TNM	Tumor, Node, Metastasis

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INTRODUCTION

Gastrointestinal Stromal Tumor (GIST) is the name given to a subset of uncommon neoplasms seen in the gastro-intestinal (GI) tract. Even though they comprise <1% of all GI tumors, GISTs are the commonest *mesenchymal* tumors of the gastrointestinal tract.[1]

GISTs are seen through the length of the GI tract – from the esophagus to the rectum.

Tumors that had been previously recognized as leiomyoma and leiomyosarcoma are actually CD117 (KIT) + tumors now called GIST.[2]

The knowledge of GIST has been revolutionized by advances in its molecular understanding; however, this occurred only in the late 1990s and the early part of the 21st century. The true incidence and global burden of this disease has often been underestimated in the past, but with more recently developed objective criteria to diagnose and classify GISTs, newer studies show a different picture.

HISTORY

In the 1940s, stromal tumors were mistakenly assumed to arise from cells of smooth muscle and were reported as GI leiomyomas, leiomyoblastomas, and leiomyosarcomas (True tumors of smooth muscle cells are extremely rare – examples include esophageal intramural leiomyomas and colorectal muscularis mucosae leiomyomas).

However in the 1970s, electron microscopic examination exposed that only a minority of these tumors showed smooth muscle differentiation.[1] these studies were backed up in the next decade by immunohistochemistry (IHC) – which showed that most of these tumors lacked the immunophenotypic features of smooth muscle differentiation.[1]

The nomenclature "GIST" was developed in 1983 by Mazur and Clark[3], only as a descriptive term to define intra-abdominal malignancies that were, despite not showing carcinomatous features, also failed to exhibit typical features of either neural/smooth muscle cells.

Herrera et al., in 1984 described a subgroup of these neoplasms that showed clear autonomic neural differentiation GANT (Gastrointestinal Autonomic Nerve Tumors).[4,5]

IHC studies in the 90's showed CD34 expression in a substantial percentage of these neoplasms. It was originally hoped that CD34 would prove to be a feature unique to GISTs. Disappointingly however, CD34 positivity was present in only half of all cases of GIST; furthermore, CD34 was not specific to GIST – it was expressed in many neural and smooth muscle tumors. Henceforth, CD34 was considered as being neither sensitive nor specific in the distinction of GIST from other mesenchymal tumors.[6,7]

The landmark advance in the understanding of GIST occurred in the late 1990s with the belief that these neoplasms showed histopathologic resemblances to the interstitial cells of Cajal (ICC), a specific cell type of the GI tract.[8] ICCs are present in the myenteric plexus and muscularis propria and function as pacemaker cells that coordinate peristaltic movements of the GI tract by acting as an intermediate link between the smooth muscle cells of the intestinal wall and the autonomic nervous system.

On electron microscopy, GIST cells and ICCs were found to have ultrastructural similarities, showing a combination of neural and myogenic differentiation, with both cell types expressing the KIT receptor tyrosine kinase (KIT RTK); consequently, it has been accepted that the precursor cells for both GISTs and normal ICCs are the same.[9,10]

The molecular aspects of GIST pathogenesis was revolutionized in a study made by Hirota et al.[11] in Japan in 1998. This group was interested in the role played by KIT in ICC and they went on to outline the association between GIST and KIT proto-oncogene mutations that initiated tumorogenesis by uncontrolled activation of the KIT signalling enzyme.

Before 2000, therefore, there were no clearly defined, objective criteria to classify GIST. Similarly, many true GIST cases were classified by other names, such as *leiomyomas, leiomyoblastomas, leiomyosarcomas, GANT (Gastrointestinal autonomic nerve tumor), Gastrointestinal pacemaker cell tumor, Plexosarcoma and Gastrointestinal neurofibrosarcoma*. This makes the interpretation of publications before the year 2000 difficult.[1]

REWIEW OF LITERATURE

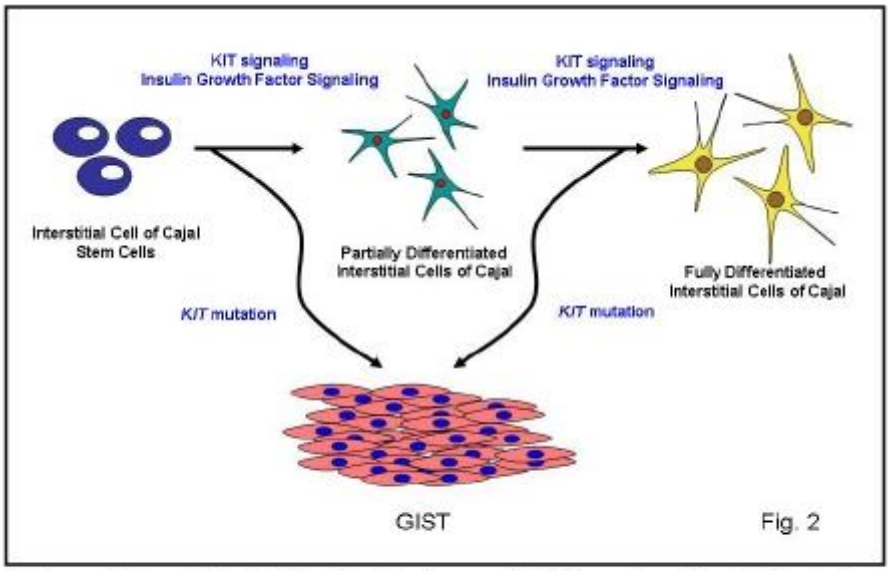
TERMINOLOGY AND DEFINITION

Gastrointestinal stromal tumors are defined as GI tract mesenchymal tumors that are specific, largely *Kit* (CD117)-positive which are Kit or platelet-derived growth factor receptor Alpha (PDGFRA) mutation-driven with typical histologic features such as spindle cell, epithelioid, and rarely pleomorphic morphology. GISTs encompass tumors with a wide spectrum of biologic potential at all sites of their occurrence.[12] The range starts from tiny, mitotically inactive, clearly benign-looking tumors (which were previously often designated as leiomyomas). At the other end of the spectrum there are larger tumors many of which contain significant mitotic activity and are histologically sarcomatous, previously often called leiomyosarcomas. In the middle, nearly all variations of tumor size and mitotic activity occur, except that the small (<2 cm) tumors with high mitotic activity are very rare.[13] Some, if not all authors maintain that most if not all GISTs should be considered having at least some potential for malignancy. GISTs are the most common mesenchymal tumor seen in the GI tract.[1]

MOLECULAR PATHOLOGY

HISTOGENESIS

Gastrointestinal stromal tumors originate from ICCs or their precursors. ICCs are intermediary cells, lying in-between smooth muscle cells that regulate motility of the GI tract and autonomic nerve function and the autonomic nervous system of the GI tract.[8] They exhibit Kit and Kit-ligand (stem cell factor) positivity. ICCs are dependent cells, which are found around the myenteric plexus as well as in the muscular layer during the course of the gastrointestinal tract. Cajal cells are/contain a subclass of totipotent stem cell-like cells that possess the ability to differentiate into smooth muscle cells when Kit signalling is disrupted.[14]



Pathway of interstitial cell of Cajal maturation and GIST formation. Interstitial cell of Cajal stem cells mature to partially differentiated and later fully differentiated interstitial cells of Cajal under the influence of KIT signaling and insulin growth factor signaling and likely many other growth and development factors. KIT or mutation in other genes such as platelet-derived growth factor receptor A leads to GIST formation.

Fig.1 Cajal cell maturation and consequent GIST formation

It has been shown that, in mice with Kit or stem cell factor deficiency intestinal dysmotility due to lack of ICCs.[15] Transgenic studies done on mice with introduced constitutional *KIT*-activating mutations was shown to cause ICC proliferation leading to GIST formation. [16,17] Kitamura and Hirota first reported *KIT* mutations in GIST in 1998 based on similarity to the mast cell system, wherein deficiency of *KIT* caused dearth of mast cells; and activating mutations was noticed to produce mast cell neoplasia.[18]

PATHOGENESIS

Mutually exclusive mutations in Kit or PDGFRA receptor tyrosine kinase proteins are seen in >80% of GISTs, which are principal in the pathogenesis of sporadic GIST. These somatic mutations are present only in cells of the tumor tissue, while the analogous constitutional mutations of familial GISTs, (which are inheritable) are present throughout all cells of the body. These mutations produce functional alterations in the Kit proteins and PDGFRA proteins, and

lead to activation.[18.19] The *KIT* and *PDGFRA* genes code for the correspondingly termed homologous receptor tyrosine kinase proteins. They (*KIT* and *PDGFRA* genes) are located pericentromerically at Chromosome 4q12, most probably having evolved as an ancestral gene duplication.[20] The analogous Kit/ PDGFRA proteins have essential features of type 3 receptor tyrosine kinases.[21] Activating *KIT*/*PDGFRA* mutations allow phosphorylation of the receptor TKs, activating downstream effectors. The final result of this activation is increased cellular proliferation and decreased apoptosis, culminating at neoplastic change (The exact genetic events are currently unknown) .[18, 19] Other genetic alterations have been identified in GISTs apart from receptor tyrosine kinase mutations. In one condition, there is possibly early tumor suppressor gene loss in chromosomes 14q and 22q, possibly pathogenetically important (Identification of specific genes have not yet been reported).[22,23]

KIT MUTATIONS

Sporadic GISTs show *KIT* mutations in four different regions of the gene. The most common is exon 11 mutation, followed by exon 9, exon 13, and exon 17 in decreasing order. The majority of Kit-mutant proteins are sensitive to the

tyrosine kinase inhibitor imatinib. But, exon 17 Kit-mutants in GIST show primary resistance. Also, exon 9 mutants have been found to be less sensitive than exon 11 mutants.[24]. In-frame deletions of one to several codons account for 60-70% of *KIT* exon 11 mutations.[25] *KIT* exon 11 missense point mutations are seen in 20-30% of GISTs. Exon 11 missense mutations in stomach GISTs have been shown to have better prognosis than tumors with exon 11 deletions.[26,27]

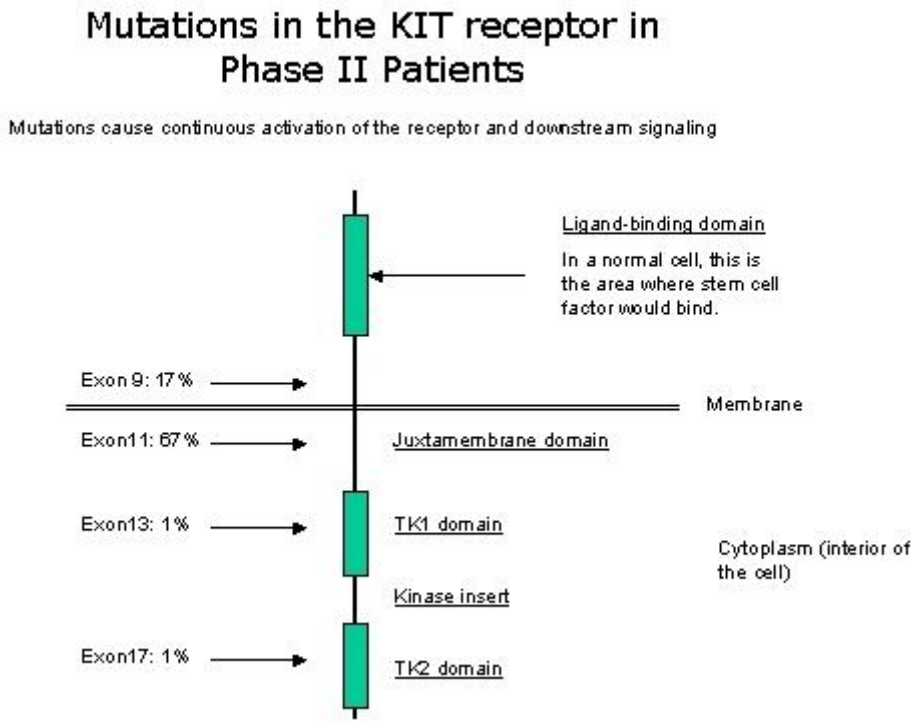


Fig.2 KIT receptor mutations

PDGFRA MUTATIONS

PDGFRA mutations occur in 3 reigions, forming GISTs. The commonest is exon18, followed by exon12 and exon14.[28] Gastric GISTs are more associated with PDGFRA mutations, usually showing epithelioid histopathology. Most (>80%) of PDGFRA mutants are missense mutations involving exon 18.This mutation shows imatinib resistance.

EPIDEMIOLOGY

Population-based studies in Iceland and Sweden show the incidence of GIST to be 11 per million - 14.5 per million.[29,30]. GIST prevalence is expected to be higher, as a high proportion of patients not succumb to the disease. GISTs show predilection for adults > 50 years of age. The median ages in most international series are slightly around 60 years. No clear sex predilection has been observed, however, men are slightly more suspectible to malignant GISTs. GIST patients who are less than 40 years of age account for 5-20% of cases in different sites. These tumors are extremely rare in the pediatric age group (<1%), where they mainly affect female young adults, are usually gastic GISTs, and often have epithelioid histopathology. Pediatric tumors may possess a dissimilar pathogenesis than adult GISTs: *KIT* /*PDGFRA* mutants are usually absent.[31,32]

GISTs are seen from the esophagus to the rectum. They are most commonly Gastric (60%), jejunoileal (30%), duodenal (5%), and colorectal (<5%).[1,13] Only few cases (<1%) have been reported in the esophagus and appendix. Gastrointestinal stromal tumors can occur in the mesentery, omentum and retroperitoneum, where they could be metastatic or possibly detached from their GI tract origin. However, a small number of apparent primary tumors have been reported in these sites.[33,34,35] A few GISTs also are diagnosed as disseminated abdominal tumors.

CLINICAL FEATURES

The clinical features associated with a GIST depend on various factors, such as the location/size of tumor/tumor behaviour. Gastrointestinal tract bleeding is commonest presentation of GIST in international literature.[1,2] This may manifest as hematemesis, melena or chronic blood loss. Tumor rupture, gastric outlet/intestinal obstruction, or intraperitoneal bleeding can simulate an acute abdomen. Smaller GISTs are often diagnosed incidentally during surgery, imaging, or endoscopy; the latter applies especially to situations where mass screening for carcinoma stomach is being practiced (Such as Japan).

Clinical features associated with GIST are similar to the pathology associated with the anatomic location of the primary tumor.

Approximately 25% of stomach and 50% of small bowel GISTs are malignant on clinical grounds. Metastases are usually hepatic or peritoneal; rarely skeletal, lymph nodal and pulmonary.[36] Metastases can develop late, even more than a decade after the curative surgical intervention, thus necessitating long-term vigilance.

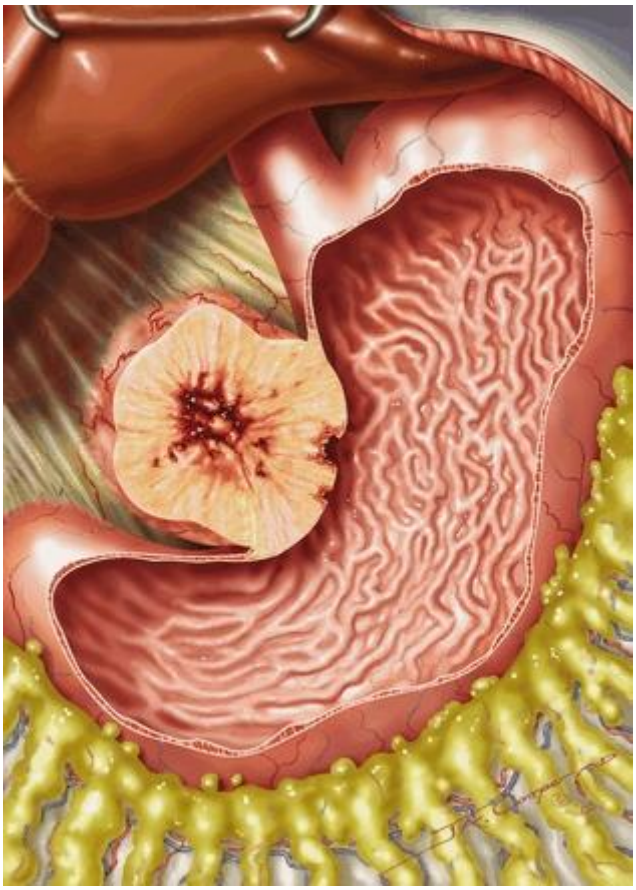


Fig 3. Typical appearance of a gastric GIST

Gastric GISTs initially start in the submucosa and usually grow slowly. Smaller tumors can manifest as incidental findings on investigations, although they occasionally may ulcerate and cause impressive bleeding. Larger neoplasms can

cause symptoms of loss of appetite and weight, pain, early satiety, and haemorrhage. Symptoms of Gastric Outlet Obstruction (GOO) may be present in lesions close to/involving the pylorus. An abdominal mass may be palpable. Metastasis is by the hematogenous route, often to liver and/or lung, although positive lymph nodes are occasionally seen in resected specimens.

Gastrointestinal stromal tumors comprise up to 15% of all small bowel malignancies. Most patients present in their fifth or sixth decade of life. GISTs are also a rare cause of primary mesenteric/peritoneal neoplasms. They may present as an abdominal mass with or without secondary symptoms.[33]

DIAGNOSTIC AND INVESTIGATIVE MODALITIES

Diagnosis is usually made by non-invasive methods such as Trans abdominal Ultrasound (USG) or Contrast Enhanced Computed Tomography (CECT). CECT is invaluable in both primary disease as well as metastatic staging.[1] Metastases to the liver are well detected by CECT; however, Magnetic Resonance Imaging (MRI) can also be used for the same.

Gastric GISTs are evaluated by upper GI scopy. They present as a smooth projections in the stomach covered by mucosa, which may show bleeding /ulceration.[37] The majority of GISTs arise submucosally and may grow in an

endophytic manner. Endo Ultrasound (EUS) is also useful in evaluation of gastric tumors.

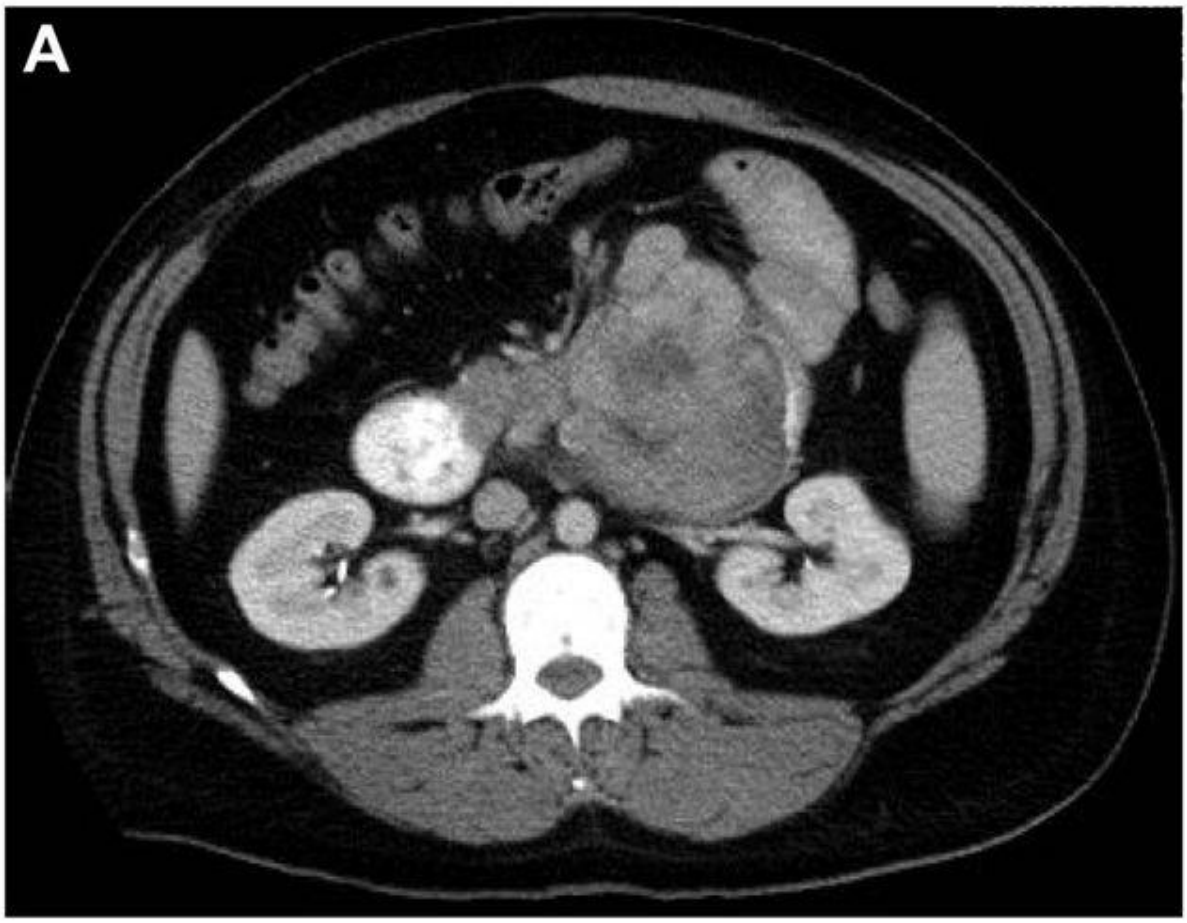


Fig.4 Gastric GIST on CECT

CT scanning provides good imaging of the tumour size as well as loco-regional involvement. Smaller sized neoplasms appear well marginated and are hypo dense on plain CT. Contrast studies show the enhancement to be homogeneous. GIST on CT may resemble other malignancies such as bowel lymphoma. Many Larger GISTs show cystic changes, surrounded by tumor enhancement on

CECT. The tumor may undergo necrosis, causing fistula formation with the bowel and/or intratumoral calcified areas.

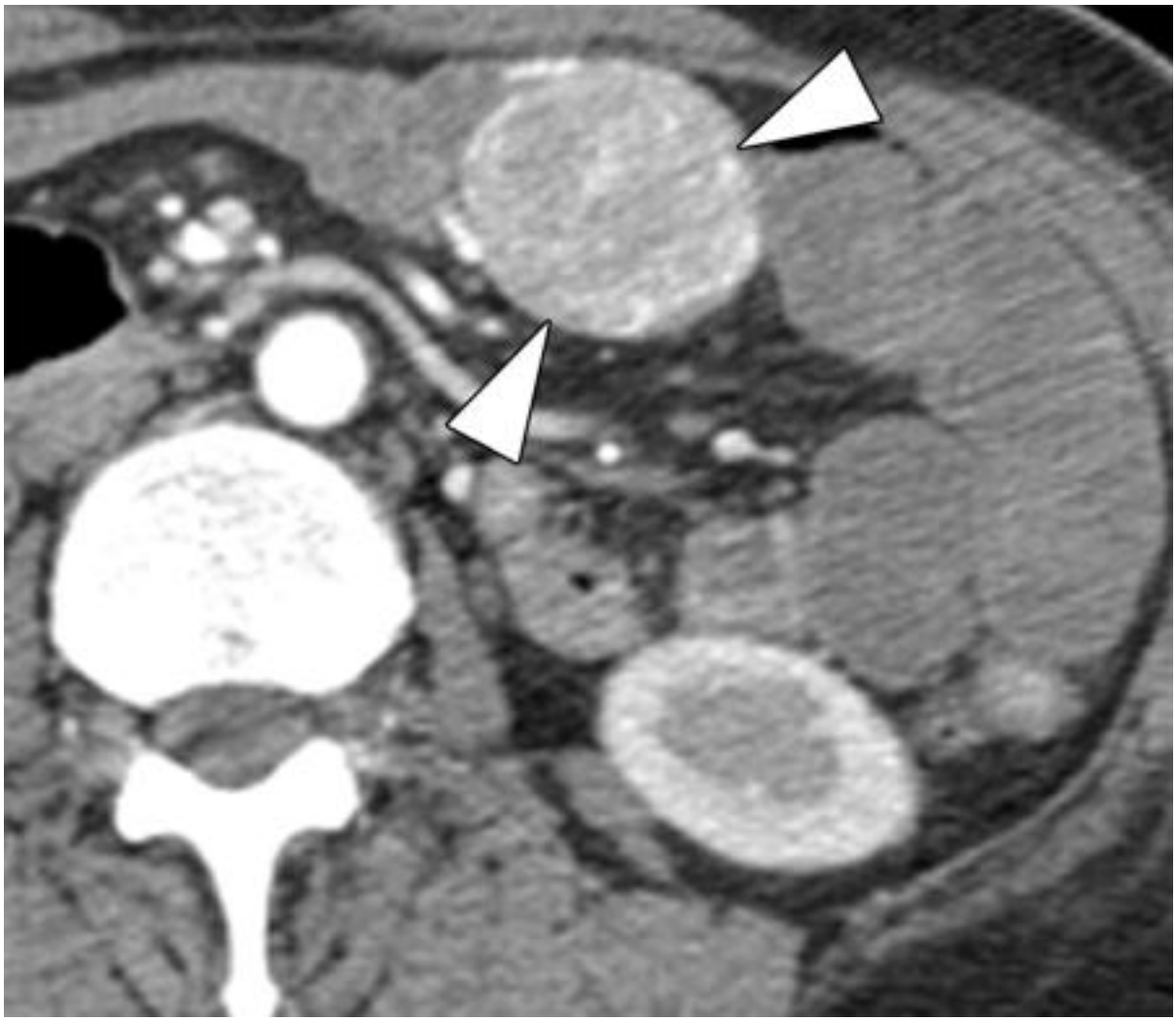


Fig 5. Jejunal GIST on CECT

Positron Emission Tomography, especially in combination with CT/MRI (PET-CT/PET-MRI) has a role in the investigation of GISTs, especially in a the event of metastasis/recurrence, or to assess response to Imatinib therapy, but the exact

role that these modalities play will be seen in the future, as the results of many ongoing trials come to light.

Preoperative biopsy is amenable only to superficial stomach lesions; via upper GI scopy.[1] Biopsies can be taken percutaneously, but this can theoretically cause seeding of the tumor into the peritoneum, or even rupture of the tumor. It should be done only in cases of certain inoperability or when different treatment may be required (e.g. the swelling proved to be a lymphoma or germ cell tumor). Peroperative frozen section is rarely indicated; as a diagnosis is likely to be given only by a highly experienced pathologist.[36]

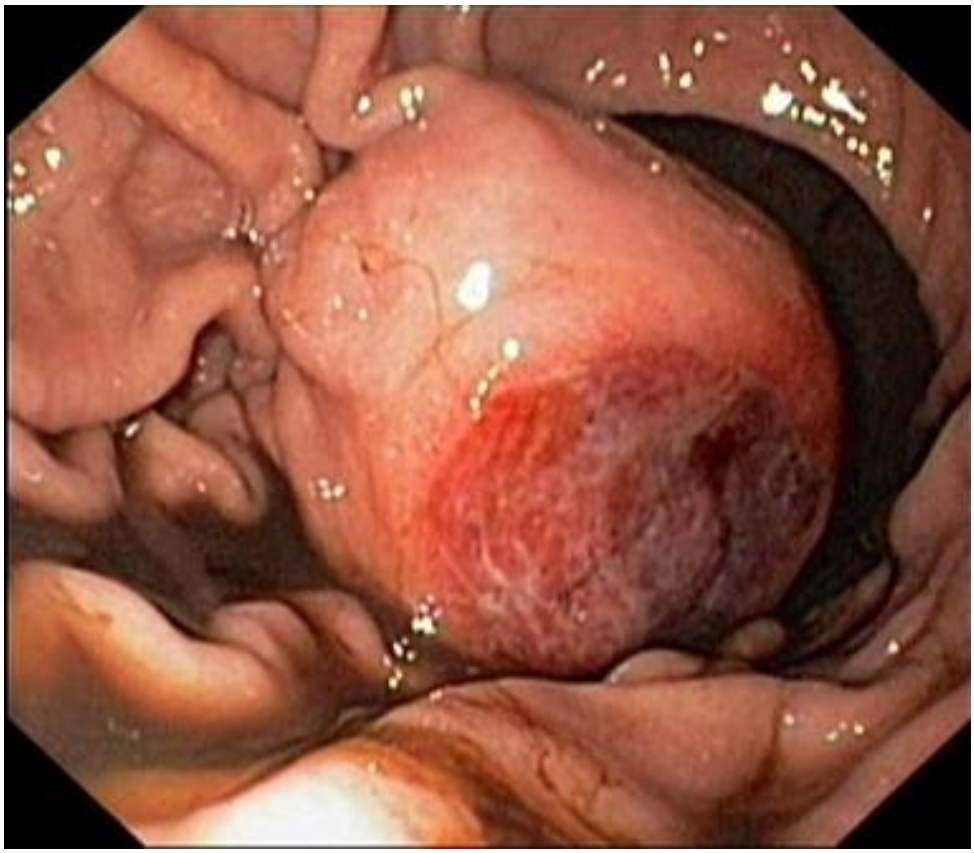


Fig. 6 Endoscopy of a gastric GIST with ulceration

HISTOPATHOLOGY

GROSS APPEARANCE

Smaller GISTs usually manifest as solid subserosal, intramural, or rarely polypoid masses, lying intraluminally. Most large GISTs form external tumors, which may occasionally be pedunculated masses attached to outer aspect of GI tract, with muscle layer involvement. Larger tumors often show cystic changes centrally. Others can depict a diverticulum-like appearance, due to communication of the external tumor with the bowel lumen by a fistulous tract. A few GISTs may show an asymmetric hourglass-like shape with a larger external and smaller internal component.

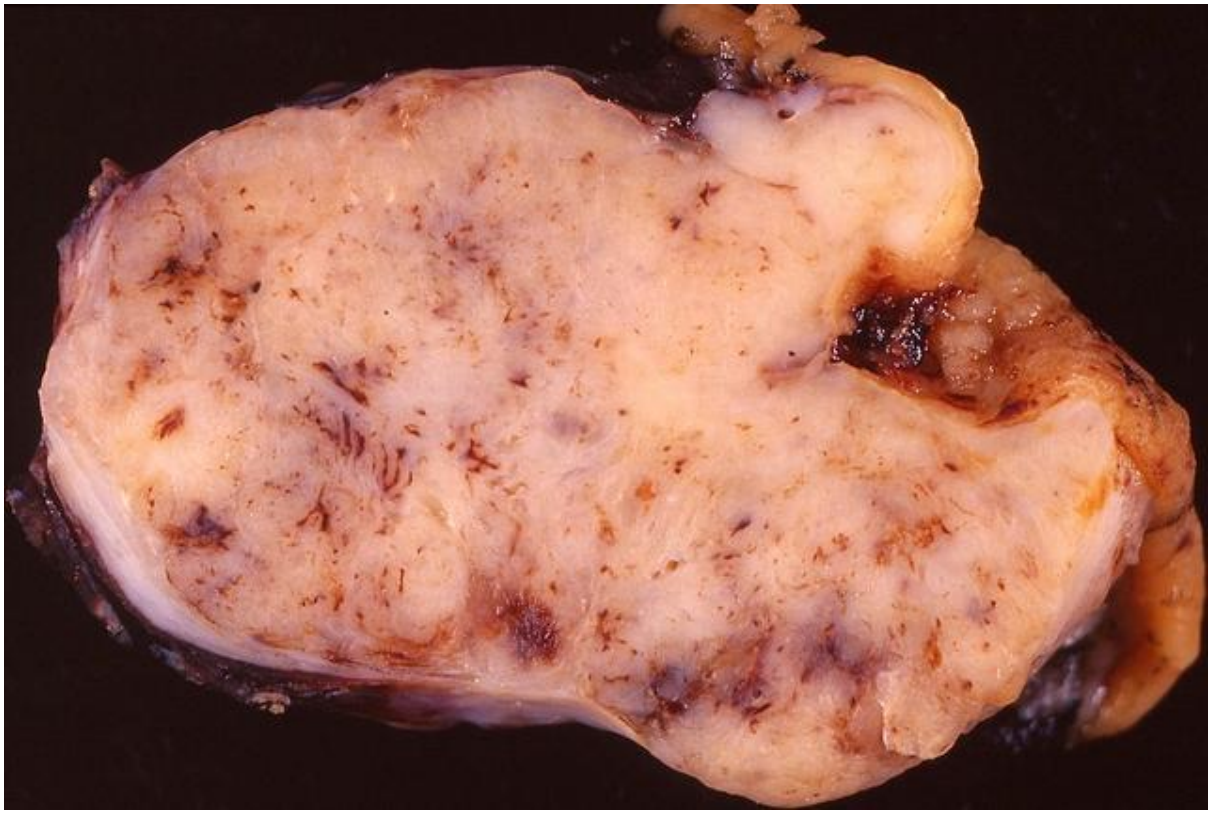


Fig. 7 Cut section of a small bowel GIST

HISTOPATHOLOGY OF STOMACH GISTs

70% of stomachs GISTs are sub classified histopathologically into 8 subtypes - 4 related to spindle cell and 4 related to epithelioid tumors. These subtypes form a spectrum.[26]

GISTs with *Sclerosing spindle subtype* are paucicellular tumors with low mototic activity. *Palisading-vacuolated subtype*, which is the most common among stomach GISTs exhibits prominent perinuclear vacuolization and nuclear

palisading, similar to peripheral schwannomas. These tumors can reach sizes > 10 cm despite having low mitotic counts. Densely packed, uniformly placed spindle cells without significant atypia and mitotic activity are seen in the *Hypercellular subtype* (Figure 2, C). Significant mitotic activity (usually >20 per 50 HPFs) and diffuse atypia is seein in the *Sarcomatous spindle cell subtype*.[2]

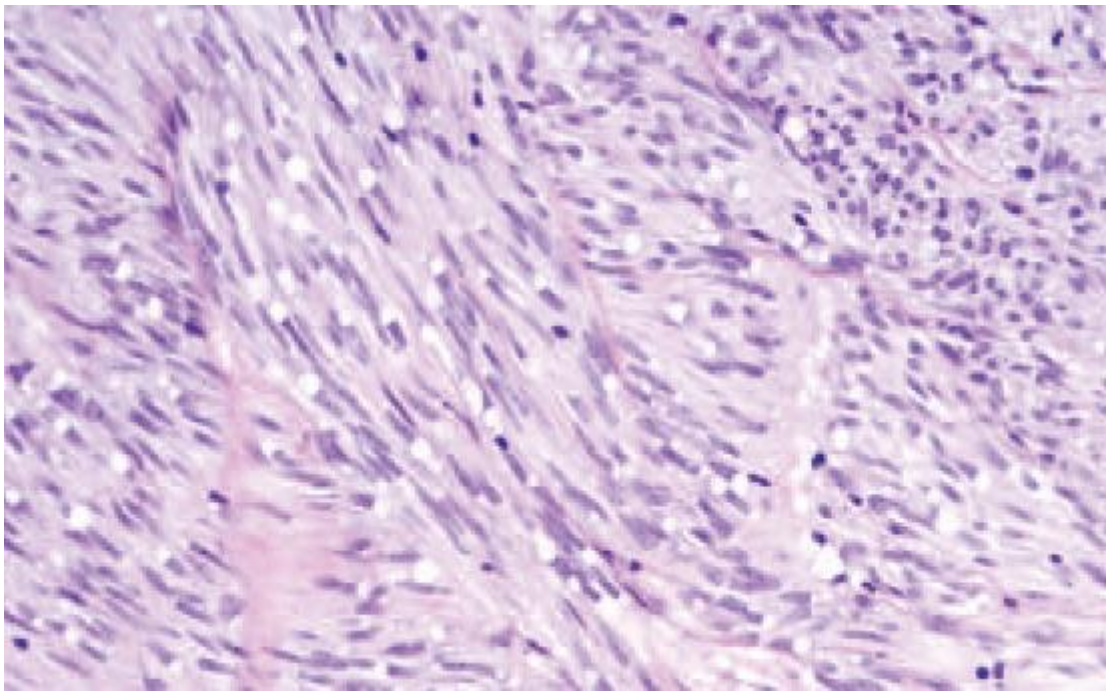


Fig. 8 Palisaded vacuolated spindle cell gastric GIST

Sclerosing epithelioid variant show low mitotic rate, however focal atypia and multinucleation are seen. The have polygonal tumors cells arranged in a syncytial pattern.

Dyscohesive epithelioid subtype exhibit a lacunar space surrounding the epithelioid cells, which have sharp cell borders. *Hypercellular epithelioid subtype* show closely arranged cells and low mitotic activity. S*arcomatous*

epithelioid also are highly cellular, but showing striking mitotic activity, often > 20 per 50 HPFs.[2]

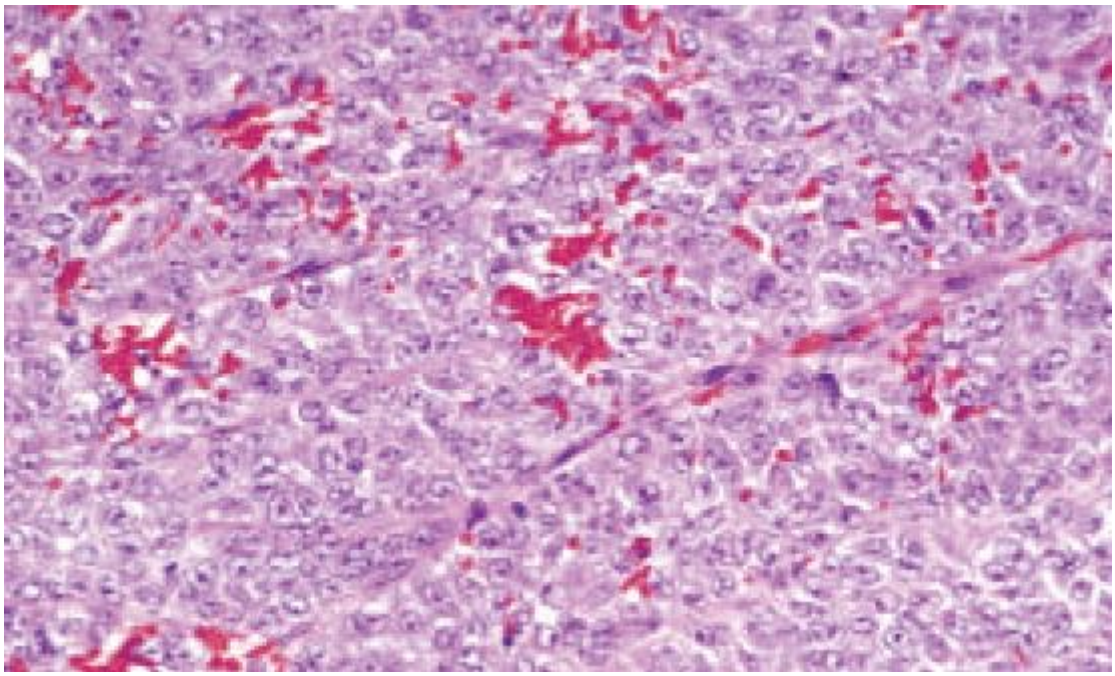


Fig.9 Sarcomatous epitheloid gastric GIST

HISTOPATHOLOGY OF SMALL BOWEL GISTs

Small bowel GISTs do not show individual histopathological subtypes appreciated in their stomach counterparts. The majority of small bowel GISTs are composed of spindle cells, and 40-50% of them show distinct, eosinophilic extracellular collagen fiber aggregates that stain positively for PAS. These aggregates are named ‘skeinoid fibers’.[39] Presence of skenoid fibres is a favorable prognostic feature, they are usually seen in nonmalignant GISTs.[40]

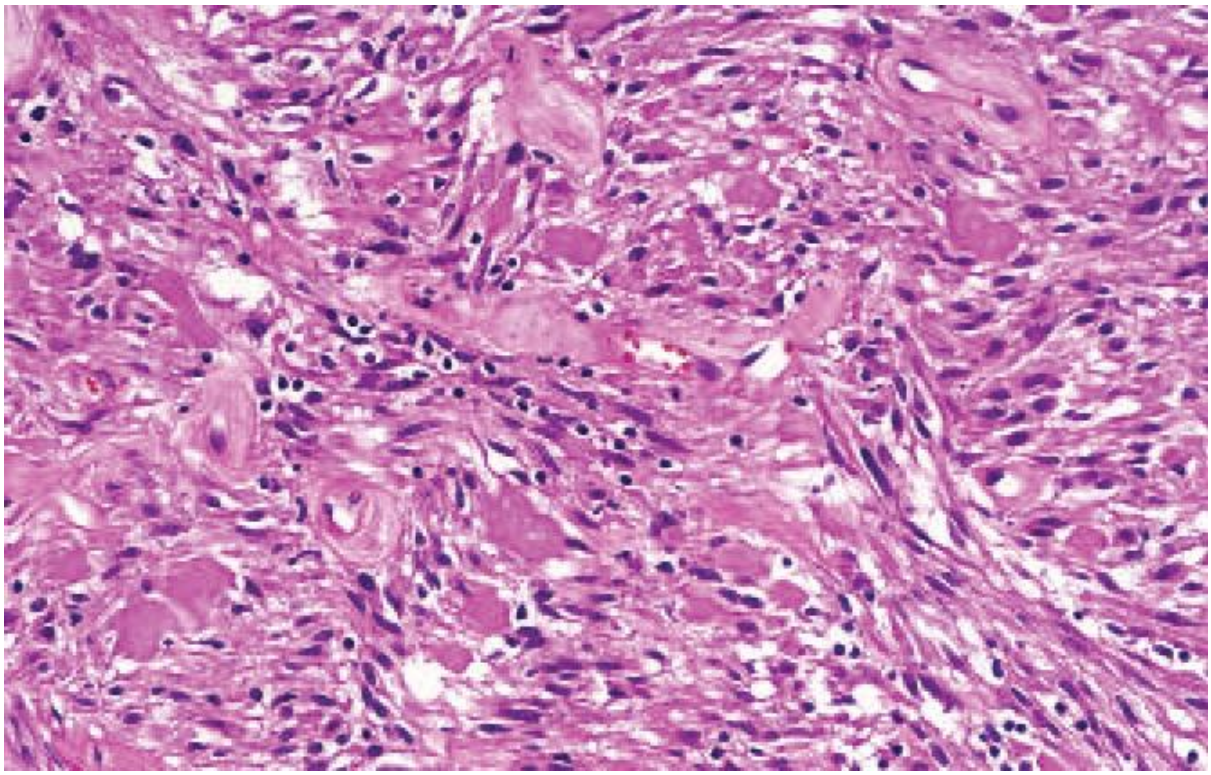


Fig. 10 Small intestinal GIST rich in skeinoid fibers

Despite the typical malignant course, only a few small bowel GISTs exhibit sarcomatous features. High mitotic activity is also uncommon. Epithelioid tumors are associated with malignant GISTs.

HISTOPATHOLOGY OF OTHER GISTS

Non-gastric, non-intestinal GISTs are usually show spindle cell histology. Rare appendiceal and some colonic GISTs show skeinoid fibers resembling small bowel tumors. Skeinoid fibers are not seen in rectal GISTs, which bear more resemblance to gastric tumors, with a hyalinized-calcified or palisading nuclear pattern. Rectal GISTs may be clinically indolent, again, similar to stomach tumors.[41]

Omental GISTs may show spindle cell and epithelioid features, similar to stomach GISTs, while mesenteric GISTs sometimes show skeinoid fibers and resemble the small bowel tumors.[33] Therefore, it is possible that omental and mesenteric GISTs represent tumors that may have detached from their GI origin (stomach and small bowel respectively) during their development.

IMMUNOHISTOCHEMICAL FEATURES OF GIST

Kit (CD117) positivity is a key feature of GIST, seen in > 95% of cases. A positive repot of CD 117, while being a chief defining principle for GIST, is no longer regarded as a categorical prerequisite. As mentioned earlier, Kit manifestation in GIST is not the result of a mutation, but is constitutional. CD34 and nestin are also expressed in GISTs. Smooth muscle indicators (eg. SMA) may be positive but GISTs are generally desmin-negative. Positive neural markers, such as S100 is rare. Keratin 18, rarely keratin 8, may be expressed.

KIT (CD117)

Global, strong *KIT* positivity in seen in GISTs, which appears pancytoplasmic. Membrane staining is better seen in epithelioid GISTs. Certain epithelioid gastric GISTs less may be weakly positive/negative for Kit - these exhibit *PDGFRA* mutations.

The best KIT antibodies presently available for paraffin sections of formalin-fixed tissue are polyclonal antibodies. Most monoclonal antibodies show inconsistent reaction with GISTs. Although definitional, Kit positivity is not diagnostic of GIST. Various other tumors such as mastocytomas, small cell lung carcinomas, seminomas, granulocytic sarcomas may show KIT positivity. More specifically, neuroblastomas, angiosarcomas, metastatic melanomas, Ewing sarcomas and clear cell sarcomas represent abdominal tumors that may be KIT positive.[42]

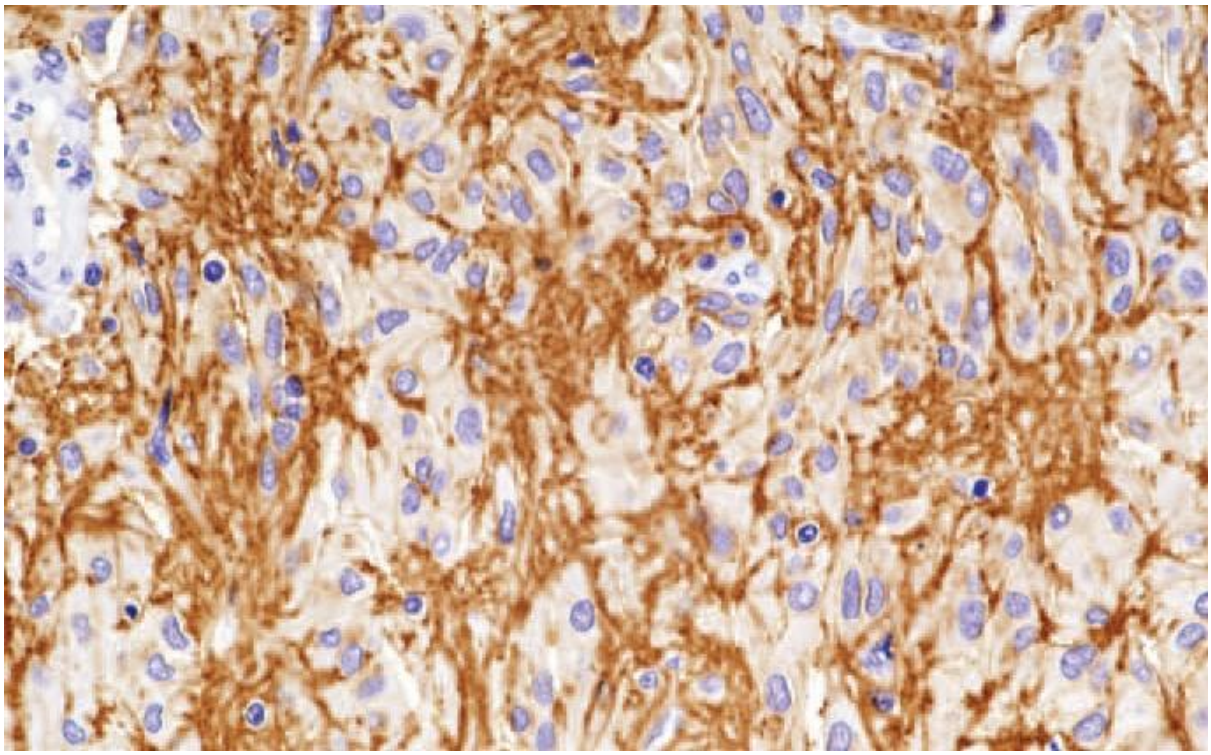


Fig. 11 KIT immunostaining in GIST

PDGFRA

Scarce data on *PDGFRA* expression is presently available. The reliability of antibodies on paraffin sections is also dismal. However, PDGFRA still can be used as a diagnostic immunohistochemical marker.[43]

OTHER GIST MARKERS

Protein kinase theta has has been suggested as an IHC tool, as well as a therapeutic kinase target for GIST.[44] However, positive staining is usually weak and less characteristic than Kit positivity.[2]

DOG1, a new gene, termed as it was ‘‘discovered on GIST’’ also is expressed in GIST and is not present in non-GISTs.[45]

80% of stomach and 50% of bowel tumors show *CD34* positivity. CD34 is a hematopoietic precursor cell antigen present in fibroblasts, endothelial cells, and related malignancies. Esophageal and rectal GISTs are nearly unfailingly CD34 positive (95-100%). [26]

DIFFERENTIAL DIAGNOSIS

Smooth muscle malignancies, desmoids, neural sheath tumours, inflammatory myofibroblastic tumors and undifferentiated sarcomas among other tumors are often mistaken for GISTs. These neoplasms almost always show Kit negativity, and most of them have their own specific immunohistochemical markers. The following table shows histological differential diagnoses for GISTs.

Table 2. Tumors That Have Been Separated From Gastrointestinal Stromal Tumor*

True smooth muscle tumors
Leiomyoma
Intramural
Of muscularis mucosae origin
Uterine-type leiomyoma in women
Glomus tumor
Leiomyosarcoma
Nerve sheath and melanocytic tumor
GI schwannoma
Metastatic melanoma
Primary GI clear cell sarcoma
Fibroblastic tumor
Desmoid
Inflammatory myofibroblastic tumor
Inflammatory fibroid polyp
Undifferentiated sarcoma

* GI indicates gastrointestinal.

Fig. 12 Histologic differential diagnosis of GIST

PROGNOSIS

GISTs, at all sites of their occurrence form a continuum in biologic potential. Older data on smooth muscle tumors of the GI tract(including GISTs in the current jargon) have created an illusion by distinctly separating benign and malignant tumors. As there were no specific separating standards, it is problematic to understand the predictive parameters based on older studies. Cancer centers have heightened emphasis on clinically malignant tumors – due to referral bias. Newer large studies (with >500 cases each) have more clearly delineated the prognostic parameters.[26,27,36] These data from the pre-imatinib era shed light on the natural history of GISTs and may help in adjuvant treatment application.

The most dominant criteria for evaluation of GIST biologic potential are tumor dimensions and mitotic activity. Mitotic activity is stated per 50 HPF (high power fields – 40x) (totaling 5 mm^2).[26,27] This corresponds to 25 fields with a x40 magnification using newer wide-field microscopes. Size and mitotic rate parameters should always be incorporated in the pathology report. There is a well-established relationship between these parameters and tumor behavior based on several large clinico-pathologic studies. There is greater biologic

potential of small intestinal versus stomach GISTs, the reasons for which are unknown.

The following table depicts prognostic criteria developed after analysis of large studies.[26,27] Lesser data on GISTs of rare sites, such as the esophagus is currently avalable. However, in terms of prognosis, tumors at these sites should probably be assessed with guidelines similar to small intestinal GISTs.

Table 3. Rates of metastases or tumor-related death in GISTs by tumor location, grouped by Tumor Size and Mitotic Rate. Adapted from Miettinen and Lasota (2006), *Seminars in Diagnostic Pathology*, 23:70-83.

Tumor Parameters			Percent of patients with progressive disease during long-term follow-up and characterization of risk for metastasis			
Group	Tumor Size	Mitotic Rate	Gastric GISTs	Jejunal and Ileal GISTs	Duodenal GISTs	Rectal GISTs
1	≤2 cm	≤5 / 50 HPFs	0% none	0% none	0% none	0% none
2	>2 cm ≤5 cm	≤5 / 50 HPFs	1.9% very low	4.3% low	8.3% low	8.5% low
3a	>5 cm ≤10cm	≤5 / 50 HPFs	3.6% low	24% moderate	34% high ‡	57% high ‡
3b	>10 cm	≤5 / 50 HPFs	12% moderate	52% high		
4	≤2 cm	>5 / 50 HPFs	0% †	50% †	§	54% high
5	>2 cm ≤5 cm	>5 / 50 HPFs	16% moderate	73% high	50% high	52% high
6a	>5 cm ≤10cm	>5 / 50 HPFs	55% high	85% high	86% high	71% high ‡
6b	>10 cm	>5 / 50 HPFs	86% high	90% high		

Fig. 13 Prognostic grouping of GIS

STAGING (TNM)

A new TNM staging system for GIST has been developed by the AJCC for GIST.[13] This is the first time that a TNM staging is being used for GIST.

This new AJCC staging is an adaptation the Miettinen and Lasota (AFIP) risk table.[26,27]

The AJCC staging schemes use "TNM" - it stands for **T**umor **N**ode **M**etastasis.

- T1 ≤ *2 cm*

  T2 > *2 cm* ≤*5 cm*

  T3 > *5 cm* ≤*10 cm*

  T4 > *10 cm*
- N0 No lymph nodes

  N1 Presence of lymph nodes
- M0 No metastasis

  M1 Metastasis present

Low grade : ≤5 mitoses/HPF

High Grade: >5 mitoses/50 HPF.[13]

Given below is the stage grouping, done separately for gastric and small intestinal GISTs.

*Gastric GIST**

Group	T	N	M	Mitotic rate
Stage IA	T1 or T2	N0	M0	Low
Stage IB	T3	N0	M0	Low
Stage II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Small Intestinal GIST***

Group	T	N	M	Mitotic rate
Stage I	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

Fig. 14 TNM Stage grouping

Grading, used in sarcomas, was earlier used for GISTs, but is not ideal , as the mitotic rates seen in GISTs is much lower. Also GISTs are more malignant at lower rates of mitoses.

TREATMENT

TREATMENT OF EARLY STAGE GISTs

Definitive surgery remains the backbone of treatment for localized, primary GIST. Surgical removal of advanced GIST should be performed only if there is an acceptably low risk of functional deficit. Large GISTs in areas that would pose a challenge to total resection (e.g., pancreatic bed invasion), should be considered unresectable; and these patients should get preoperative imatinib, and strict regular follow up should be employed. For these cases, PET scanning is very valuable for early assessment of therapeutic response. Imatinib minimizes the risk of disease progression, which may put the patient at risk for further tumor growth and invasion. After the maximal response (generally by 4-6 months), decisive surgical resection could be performed.[1]

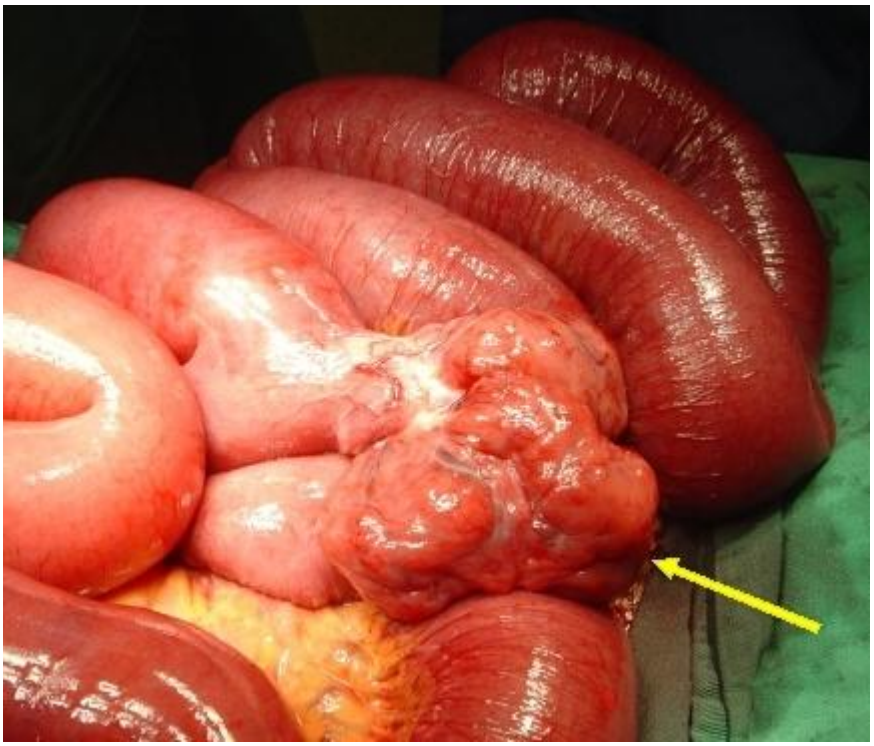


Fig 15. Intraoperative picture of a small intestinal GIST

Regarding the surgical approach to GIST resection, it must be evoked that locoregional lymph nodal involvement is rare, and so lymph node dissections are rarely indicated. GISTs sometimes have a fragile pseudocapsule; tumor rupture during surgery must be avoided, failing which, peritoneal dissemination can occur.[46] The resected margins of the specimen should be oriented and examined, and biopsies from various areas of the tumor should be examined by the pathologist.

In cases of limited, early stage GIST, a R0 resection should be performed. Preoperative Imatinib treatment can be given if complete resection is not possible.[47] Post-operatively, patients with poor prognostic criteria (mentioned earlier) should recieve adjuvant imatinib.[47,48]

MANAGEMENT OF UNRESECTABLE,METASTATIC, OR RECURRENT GISTs

Before the introduction of tyrosine kinase inhibitors such as imatinib, which became known as "targeted therapy" for treatment of GISTs, conventional cytotoxic chemotherapy was used, but with generally fruitless results. Rates of response to a variety of chemotherapeutic drugs for patients with GISTs were in the region of a paltry 0-5%.[49,50] Even intraperitoneal chemotherapy[51] was tried, again unsuccessful (Only few cases of GIST remain limited to the peritoneal surface).

Other loco-regional procedures, such as hepatic artery embolization or chemoembolization were also tried, albeit with little success. Limited progression-free survival was seen in some patients, but the benefit was usually for months rather than years, and this too lost favour in the management of metastatic/unresectable GIST patients.[52,53]

GIST showed pronounced resistance to chemotherapy – this was shown to be partly by the greater levels of P glycoprotein which is produced by the MDR - 1 gene(multi-drug resistance 1) and the MRP - 1 (multi-drug resistance protein 1).[54]

It has been hypothesized that chemotherapeutic drugs are prevented from reaching intracellular therapeutic levels in the GIST cells by these cellular efflux pumps.

Radiotherapy too has a very limited role to play in management of metastatic/unresectable GISTs - therapeutic doses of radiotherapy delivered to intrabdominal tumors generally result in more morbidity than any benefits. However, newer radiotherapy modalities such as IMRT (Intensity-Modulated Radiotherapy) can be used for palliation in specific patients. (eg. focal bleeding/pain control/bulky liver metastasis etc.)

Evidently, patients with metastatic/unresectable GIST had dismal prognosis before the introduction of mechanism-based molecularly targeted therapy. In patients with metastatic or recurrent GISTs, the majority of studies documented very poor survival rates, with mortality from disease progression usually occurring within 2 years after the first recurrence or metastasis.[36,49]

TARGETED THERAPY FOR GIST: IMATINIB

Imatinib mesylate (*Gleevec, STI-571*) was created in the 90s by Lydon and Druker, initially aimed for the treatment of hematologic malignancies, such as CML.[55,56] Imatinib is a 2 - phenyl-amino-pyrimidine derivative, acting by inhibiting many tyrosine kinases. It acts by occupying the functional *TK* site, and leads to a reduced activity by blocking entry of substrate to the kinase site.[55]

(Figure below) Imatinib was shown to be very efficacious and it is currently a record-holder, as the drug to be approved quickest by the FDA. Approximately 90 % of GISTs harbor an activating mutation in the KIT or PDGFR alpha oncogene known to confer imatinib sensitivity. Several trials have revealed that imatinib response mainly depends on the status of KIT/PDGFR alpha mutant.[55,56]

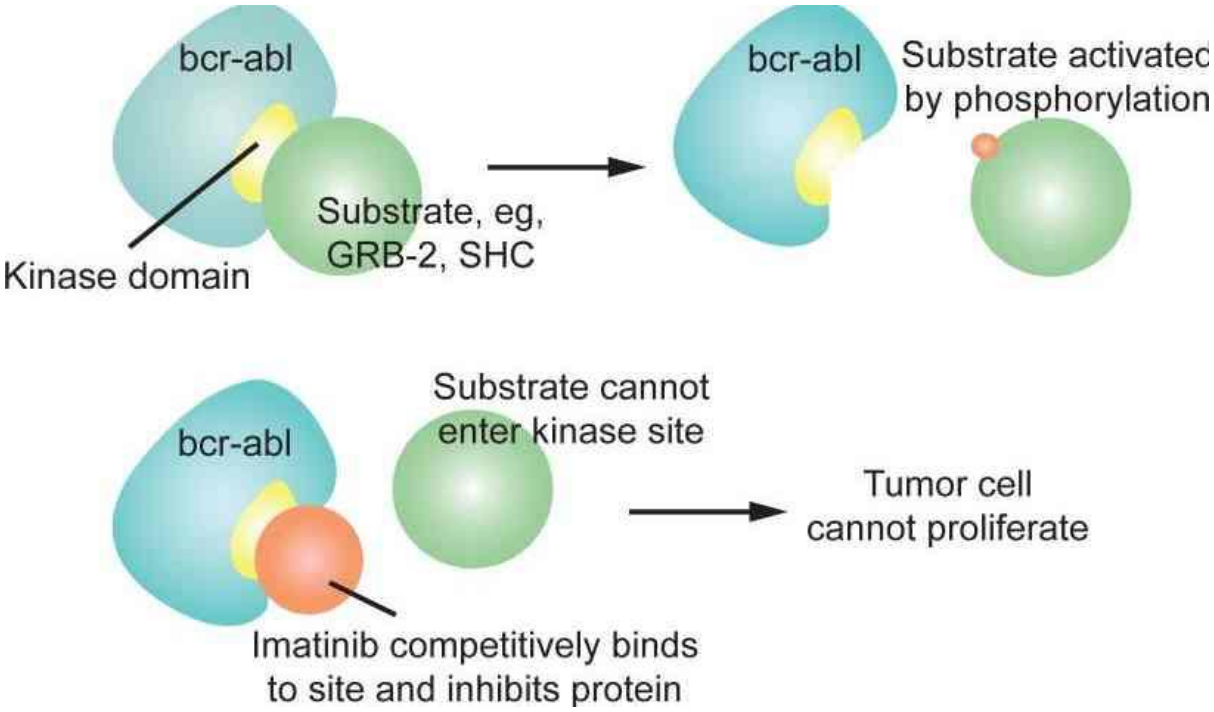


Fig 16. Mechanism of action of imatinib

Objective response with imatinib is achieved in > 50% advanced GIST; 6-months progression free survival (PFS) rate of >75 % in patients with advanced GISTs could also be achieved. Also, even in patients with stable disease, long-term tumor control could be achieved.[36,47,48]

Mulitple studies, including EORTC-62024, RTOG and the ACOSOG, amongst others have shown tremendous benefit from Imatinib in the management of GIST.[48]

Imatinib is used at a starting dose of 400 milligrams / day. For cases with KIT-exon9 mutants, the start dose is 800mg/day.[47] Imatinib plasma level studies being conducted to perfect the dose. Imatinib has a relatively good side effect profile, although most toxicities are dose-related. Uninteruppted treatment must be followed, as a break is associated with rapidly progressive disease. The ideal period of adjuvant imatinib therapy is currently unknown.[1,47]

Resistance to imatinib happens usually between 18-26 months. Other simiilar molecules have also been developed. Sunitinib, another inhibitor of TK is exquisitely efficacious in exon9 ckit mutants, which generally are poor responders to imatinib.

To monitor disease response to Imatinib, various imaging modalities were utilized, even during drug development itself. Imatinib was found to dramatically affect tumor avidity for ^{18}FDG, as seen on a PET scan. Reduced tumor avidity for ^{18}FDG could be detected on a PET scan even 24 hours-post an imatinib dose, much before a CT scan. Correlation with positive response to imatinib as well as documention of imatinib resistance was noted in studies. Thus, ^{18}FDG-PET functional imaging of GIST represents a useful technique for early assessment of response to treatment with imatinib.[57,58]

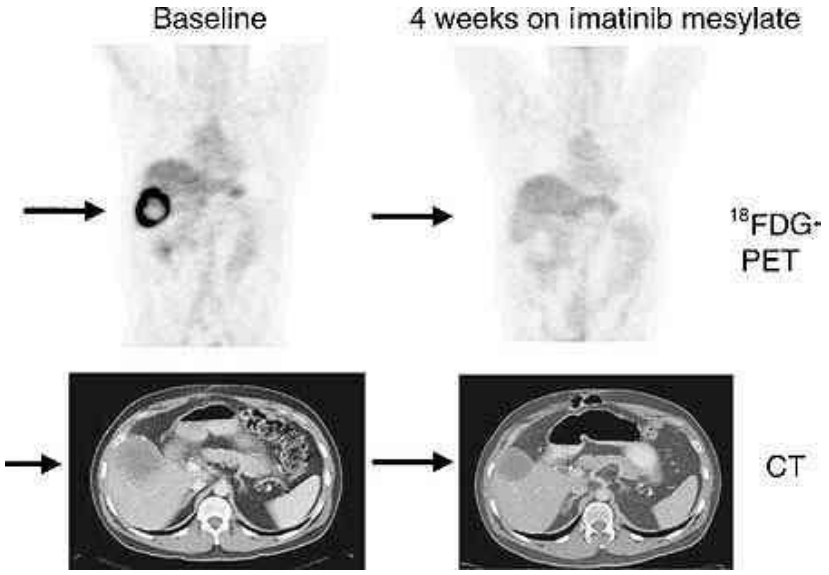


Fig. 17 Response to imatinib as imaged by ^{18}FDG-PET (above) and CT scans (below)

Although PET scans showed *metabolic* responses in the majority of patients, *Objective* responses (using RECIST criteria) were lacking. Studies have shown that a tumor shrinkage of >10% or a reduced tumor density of 15% on CT scanning before and after 60 days of imatinib identified cases with good metabolic response. This new CT criteria is called Choi criteria[59], and it helps in identification patients who have a lengthier period to progression. The Choi criteria has now been proved to be advantageous over RECIST.[59,60]

RESISTANCE TO IMATINIB

Imatinib resistance may be primary and presents itself as rapid disease progression in spite of initial imatinib treatment; however this is seen in < 20% of patients. More commonly, clonal evolution of a resistant GIST is detected >1 year of established disease-free interval. Many foundations of imatinib resistance in GIST have been described,[61,62] similar to those mechanisms demonstrated in CML.

The most commonly seen mechanism of imatinib resistance is the appearance of new mutations at a discrete region of the KIT-kinase coding area.[61,62] It is possible that previously double-mutant tumor cells could slowly grow out under the stimulus of chronic imatinib selection pressure, similar to the rise of antibiotic-resistant strains of bacteria. To deal with the double-mutant KIT molecular target, newer drugs such as sunitinib malate, which is a structurally dissimilar kinase inhibitor have been used for differential activity against the mutant. Sunitinib also exhibits potent antiangiogenesis activity as it targets several tyrosine kinases for inhibition, including the VEGF receptor in addition to PDGFR. Phase I and II trials of sunitinib showed that many patients experienced reduction of GIST activity on ^{18}FDG-PET imaging, and a large group achieved disease. However, only a minority of patients actually experienced objective response • by RECIST criteria.[84] A large trial validated

that sunitinib definitely improved the progression-free survival of patients following failure of Imatinib due to resistance/intolerance.[63]

Rare instances of Sunitinib resistance have also been reported, newer drugs such as Sorafenib are promising and under investigation.

PEDIATRIC GIST

Pediatric GISTs are rare tumors and most data has come from case reporting. They are more commonly seen in girls, above 10 years of age. GIST mutations in this population have still not been described. The majority are Gastric GISTs, showing multifocal tumors.). Nodal metastases, recurrence at previous site are more common than in adults. However disease progression is less aggressive compared to adults. [64-68]

CARNEY TRIAD

Carney Triad denotes two out of the following three tumors[69]

- GIST
- Chondromas of the lung
- Paragangliomas at non-adrenal sites

<40 cases of Carney triad have been published. Females are usually affected (>80%), and the initial malignancy appears <30 years of age in 90% of cases. The first malignancy is typically a stomach GIST.

These GISTs exhibit multi-focality. Duodenal tumors can occur. Disease aggression is lesser than sporadic cases, with comparatively better prognosis.[70]

FAMILIAL GIST

Occasionally GIST may run in families due to. This rare entity (<20 published cases) occurs secondary to germline mutations of KIT/PDGFRA genes. Patients develop the tumor at a younger age, usually in the third and fourth decade of life. It is an autosomally dominant condition.

KIT mutants show various other features, such as skin pigmentation, nevus, urticarial-pigmentosa, and achalasia may be seen.

PDGFRA mutant has not shown to have other symtoms.[71]

STUDY DESIGN

AIMS AND OBJECTIVES

AIM :

The understanding of GIST is evolving; and the specific criteria to define and classify GISTs have come into the mainstream only after 2000. This, along with its rarity makes our knowledge about GISTs relatively limited. The lacunae are *more expressed in India*, where there have been very few clinico-pathologic studies done.

The main aim of the study is to evaluate the epidemiology, clinical presentations, investigations, histopathologic features and treatment modalities of GIST.

The study was conducted by a retrospective analysis of patients who were admitted in all the surgical units of the Department of General Surgery and in the Department of GI Surgery, Govt. Stanley Medical College and Hospital, Chennai between October 2010 and October 2012

OBJECTIVES:

1) To study the epidemiology of GIST
2) To study the clinical presentation of GIST
3) To study the various treatment modalities of GIST
4) To study the histopathology and grading of GIST
5) Review of literature of GIST

Inclusion criteria:

1) Histopathologically proven case of GIST

Exclusion criteria:

None

MATERIALS AND METHODS:

Patients admitted in our hospital from October 2010 to October 2012 will be enrolled in the study. The following materials and methods were used:

- Clinical history
- General and systemic examination
- Imaging modalities (USG/CECT)
- Upper GI Endoscopy
- Surgery
- Gross pathology
- Microscopic histopathology
- Immunohistochemistry (CD117)

A total of 32 patients who were histopathologically diagnosed as GIST were included in the study.

The study design is as follows.

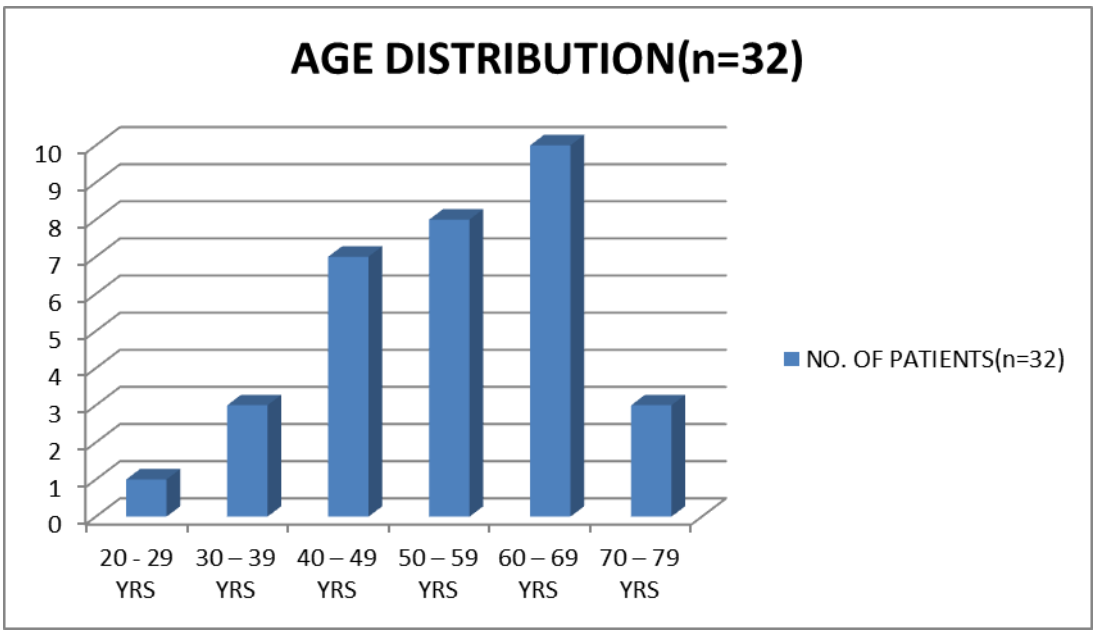
1. All the patients are subjected to detailed history taking and clinical examination
2. Patients underwent imaging modalities – Ultrasound (USG) and Contrast Enhanced Computed Tomogram (CECT), as part of diagnostic and staging workup and the findings were noted.

3. If indicated, the patients underwent Upper GI Scopy (Gastric GISTs)
4. Patients were subjected to appropriate surgery.
5. Intraoperative findings were studied.
6. The tumor specimen was sent to the Department of Pathology to study the Gross, Microscopic and Immunohistochemical pathology.
7. All the findings were tabulated in a master chart, and data analysis was done.
8. The results of the study were compared to existing Indian as well as international data.

RESULTS

AGE DISTRIBUTION:

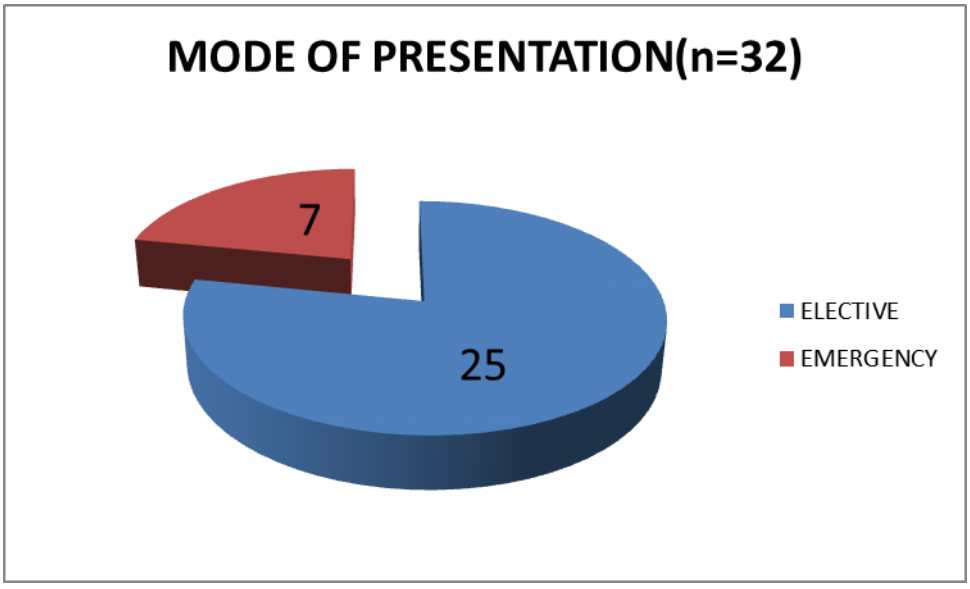
AGE GROUP	NO. OF PATIENTS(n=32)
20 - 29 YRS	**1**
30 – 39 YRS	**3**
40 – 49 YRS	**7**
50 – 59 YRS	**8**
60 – 69 YRS	**10**
70 – 79 YRS	**3**



Majority of patients were above 50 years of age (21/32), with peak incidence between the 60-69 years of age (10 patients)

PRESENTATION

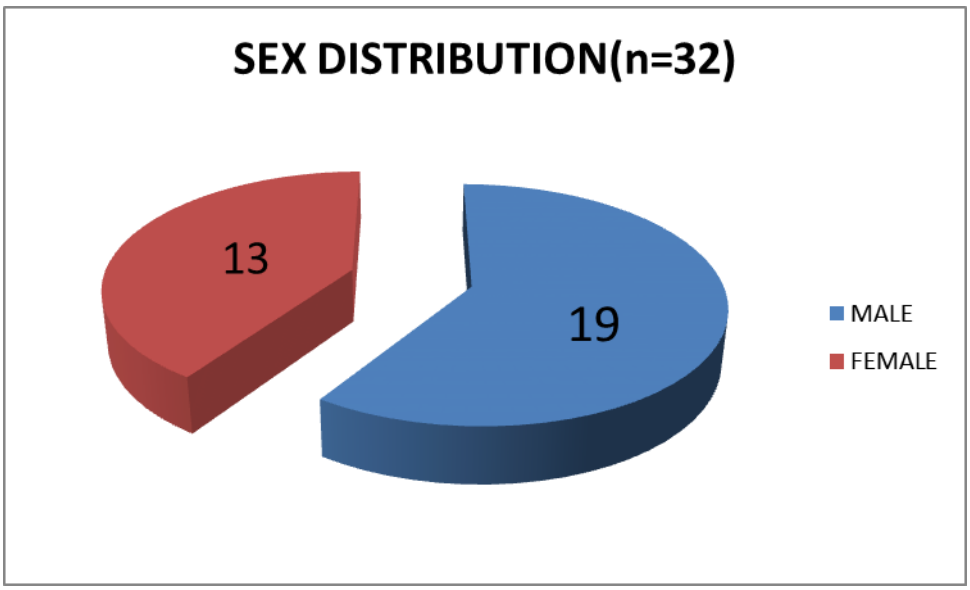
MODE OF PRESENTATION	NO. OF PATIENTS(n=32)
ELECTIVE	25
EMERGENCY	7



Out of 32 patients, 25 (78%) presented electively in the OPD, while 7 (22%) presented as an acute emergency.

SEX DISTRIBUTION:

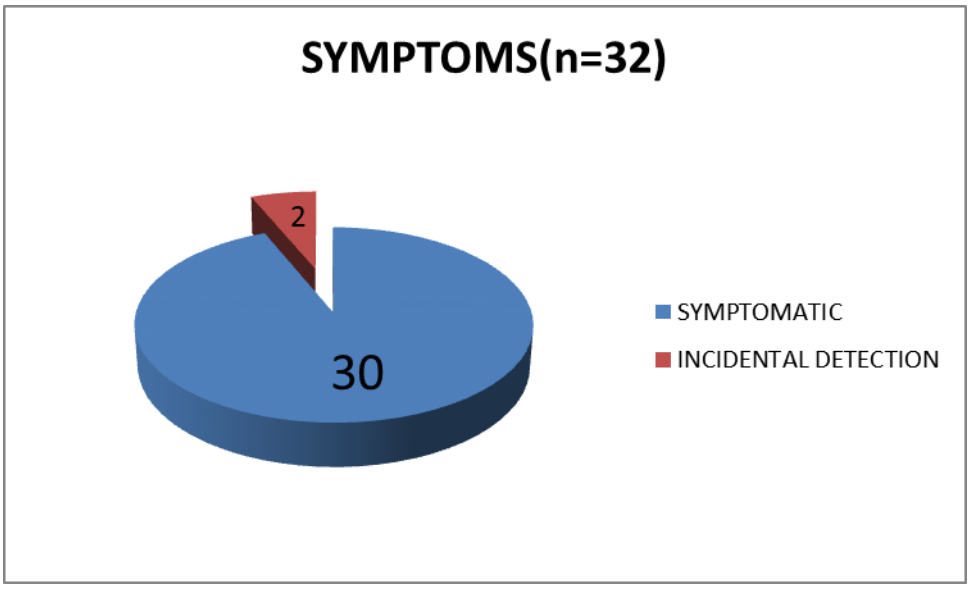
SEX	NO. OF PATIENTS(n=32)
MALE	**19**
FEMALE	**13**



19 Males comprised the majority of the patients (59.4%) with only 13 females (40.6%) in the study group.

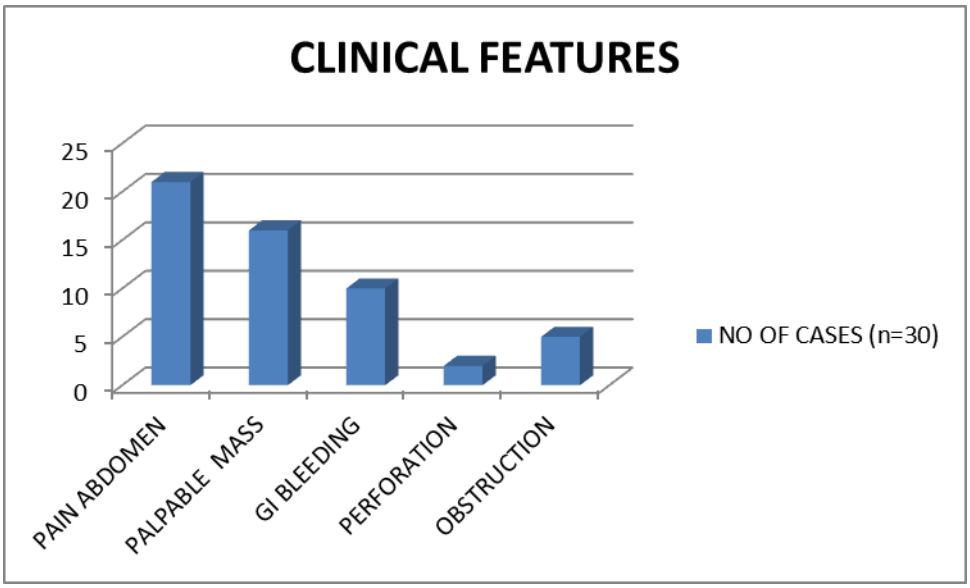
SYMPTOMS:

	NO. OF PATIENTS(n=32)
SYMPTOMATIC	30
INCIDENTAL DETECTION	2



CLINICAL FEATURES:

CLINICAL FEATURES	NO OF CASES (n=30)
PAIN ABDOMEN	21
PALPABLE ABDOMINAL MASS	16
GI BLEEDING(HEMATEMESIS/MALENA)	10
PERFORATION	2
INTESTINAL OBSTRUCTION	5

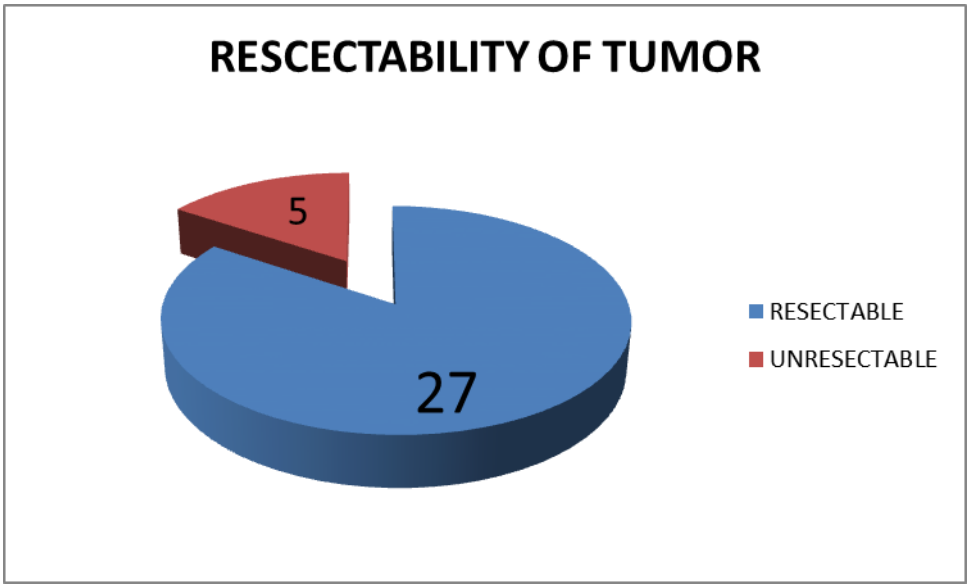


Pain abdomen was the predominant symptom, seen in 21 patients. 16 patients had a palpable abdominal mass at the time of presentation. 10 patients presented with symptoms of GI tract bleeding (hematemesis/malena).

Of the 7 patients presenting as acute emergency, 5 had features of intestinal obstruction, while 2 presented with perforation and peritonitis.

RESCECTABILITY OF TUMOR:

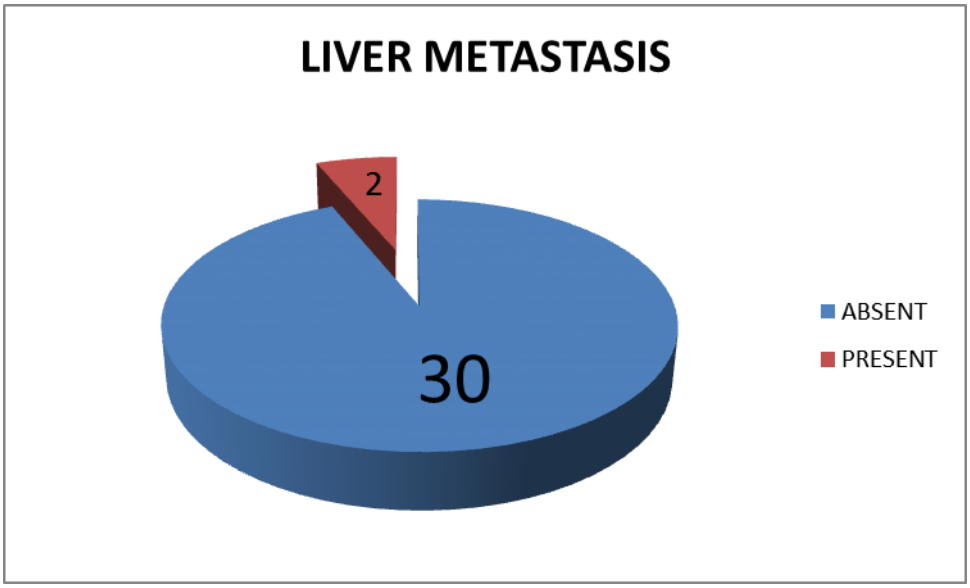
RESCECTABILITY OF TUMOR	NO. OF PATIENTS(n=32)
RESECTABLE	**27**
UNRESECTABLE	**5**



Out of 32 patients, 30 (94%) had resectable tumors. 5 patients had unresectable tumors.

METASTATIC DISEASE:

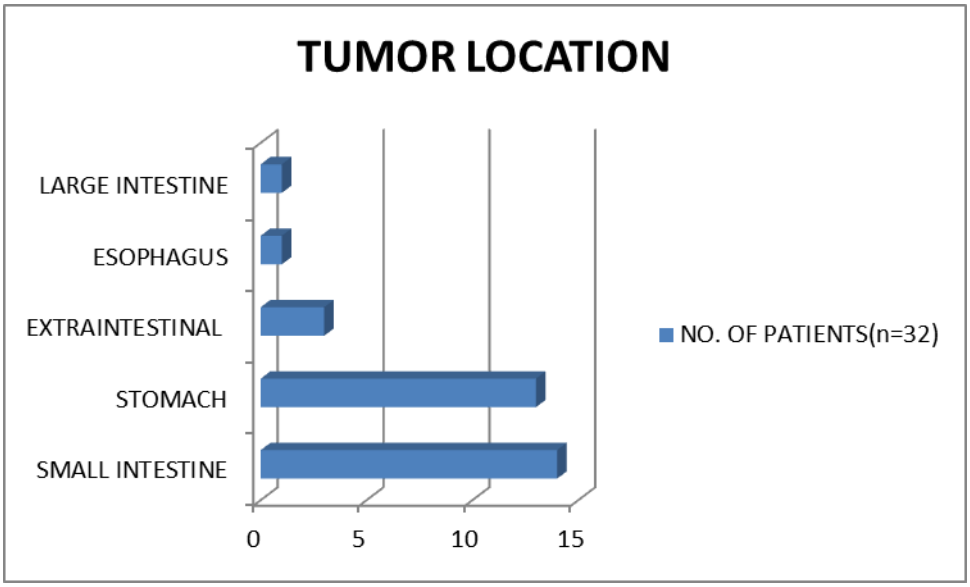
LIVER METASTASIS	NO. OF PATIENTS(n=32)
ABSENT	**30**
PRESENT	**2**



Only 2 patients presented with liver metastasis both these patients also had unresectable disease.

TUMOR LOCATION:

	NO. OF PATIENTS(n=32)
SMALL INTESTINE	**14**
STOMACH	**13**
EXTRAINTESTINAL	**3**
ESOPHAGUS	**1**
LARGE INTESTINE	**1**

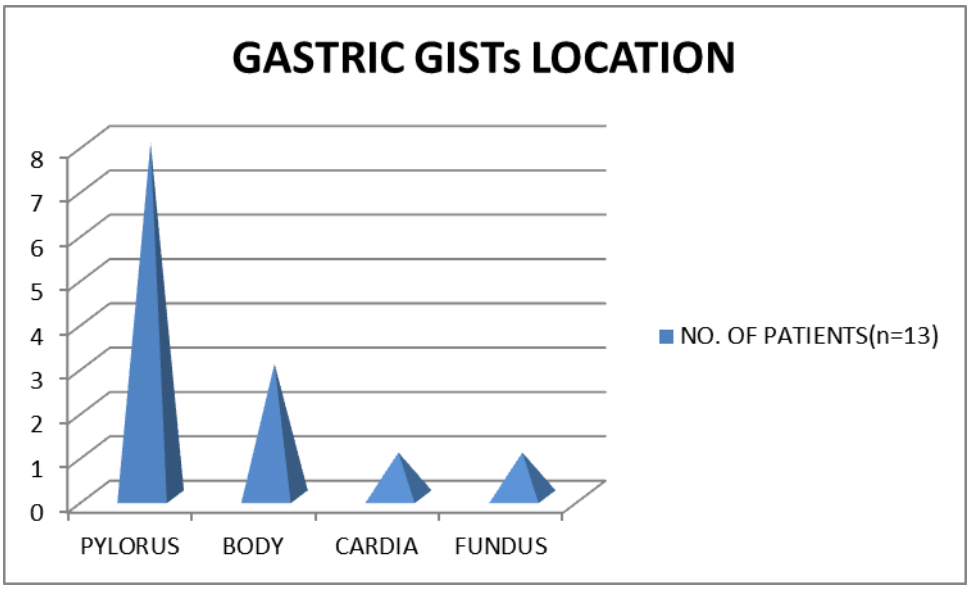


14 patients (43.7%) patients had primary disease in the small bowel. 13 patients (40.6%) presented with Gastric GIST. 3 patients had extraintestinal disease (2 patients had the primary from the ileal mesentery and another patient developed an Omental GIST).

One patient each had primary tumor localised to the esophagus (lower 1/3) and large intestine (caecum).

GASTRIC GISTs LOCATION:

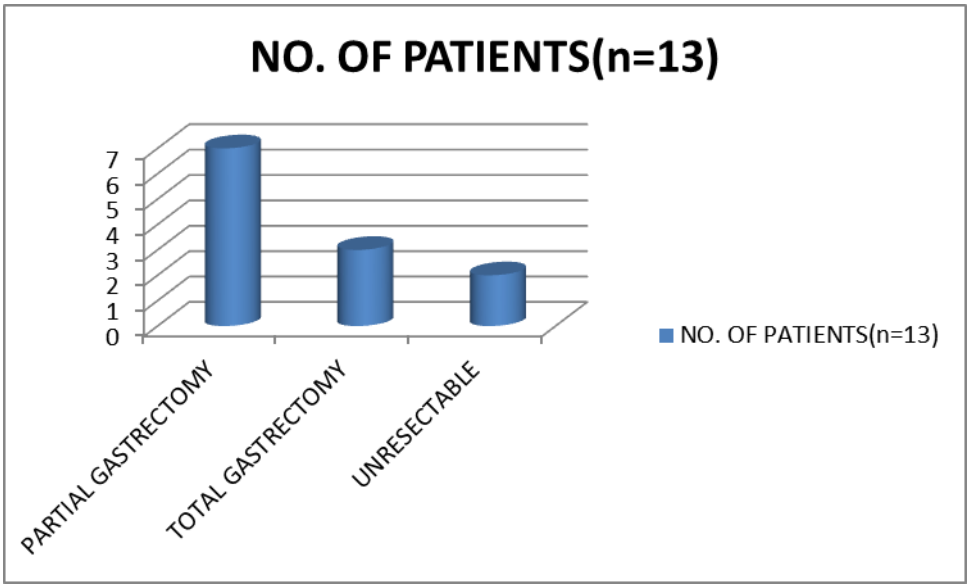
GASTRIC GISTs LOCATION	NO. OF PATIENTS(n=13)
PYLORUS	**8**
BODY	**3**
CARDIA	**1**
FUNDUS	**1**



Majority of the gastric GISTs were localised to the pylorus (8), followed by the body (3). One patient each had fundal and cardial GIST.

SURGICAL MANAGEMENT FOR GASTRIC GISTs:

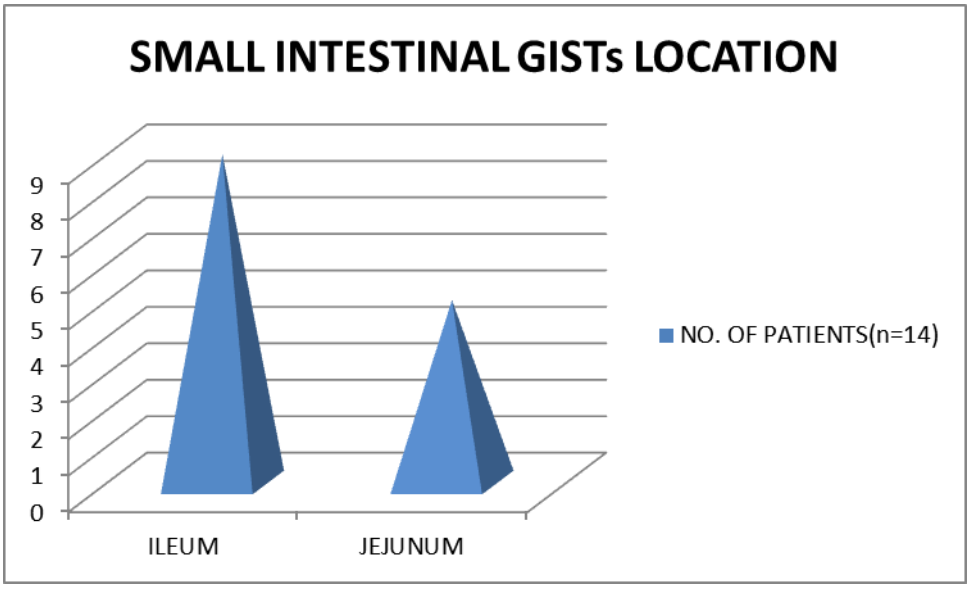
SURGERY	NO. OF PATIENTS(n=13)
PARTIAL GASTRECTOMY	7
TOTAL GASTRECTOMY	3
UNRESECTABLE	2



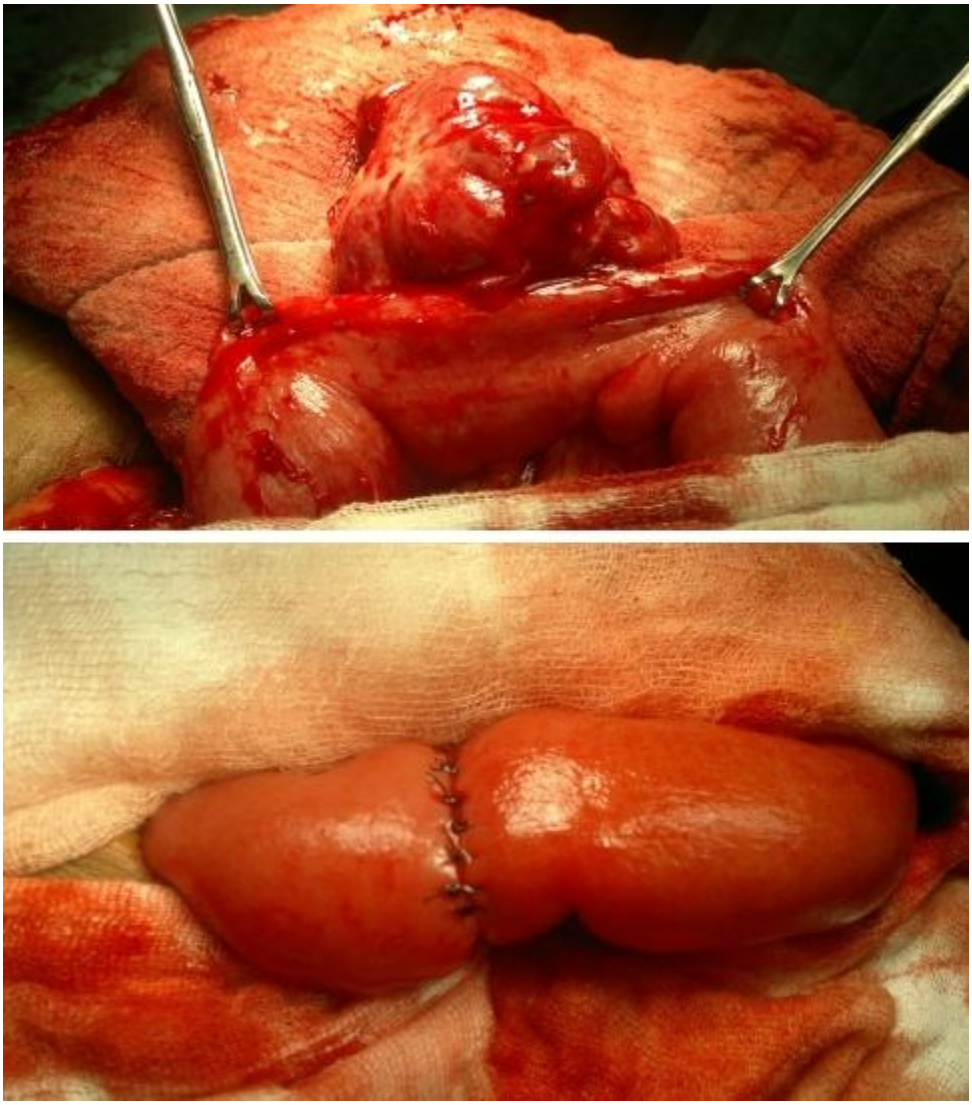
The majority of patients with gastric GISTs underwent a partial gastretomy(7), while a total gastrectomy was performed for 3 patients. 2 patients were inoperable with liver metastsis, feeding jejunostomy was done in them, as they also had symptoms of gastric outlet obstruction.

SMALL INTESTINAL GISTs LOCATION AND SURGICAL MANAGEMENT:

SMALL INTESTINAL GISTs LOCATION	NO. OF PATIENTS(n=14)
ILEUM	**9**
JEJUNUM	**5**



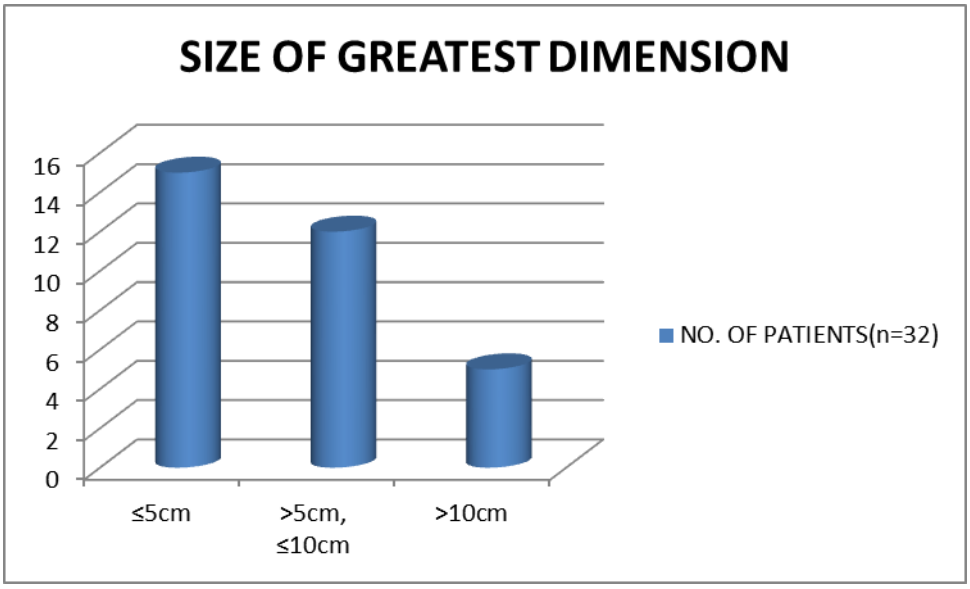
Most of the small bowel GISTs were seen in the ileum (9), while 5 patients had jejunal GISTs. All 14 patients with small intestinal GISTs were operable, and Intestinal Resection/Anastamosis was done in all cases.



Figs. 18 Jejunal GIST before and after Resection/anastamosis

SIZE OF PRIMARY TUMOR:

SIZE OF GREATEST DIMENSION	NO. OF PATIENTS(n=32)
≤5cm	15
>5cm, ≤10cm	12
>10cm	5

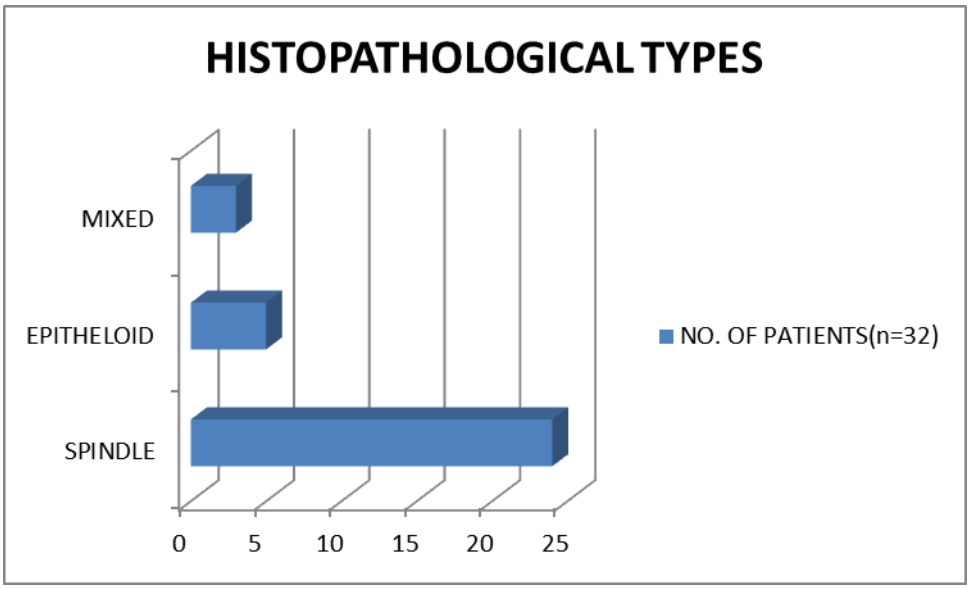


The majority of patients (15) had tumor size in the greatest dimension ≤5cm. 12 patients had primary GIST size between 5-10 cm, while 5 patients had GISTs > 10cm in size. The tumors studied showed wide variation in size, with the smallest measuring 2cm and the largest 28cm.

Median size was 6 cm. The largest GIST (28cm) was seen in the ileal mesentery. The tumor produced intestinal obstruction and was unresectable, however, debulking and intestinal resection/anastomosis was done.

HISTOPATHOLOGICAL TYPES:

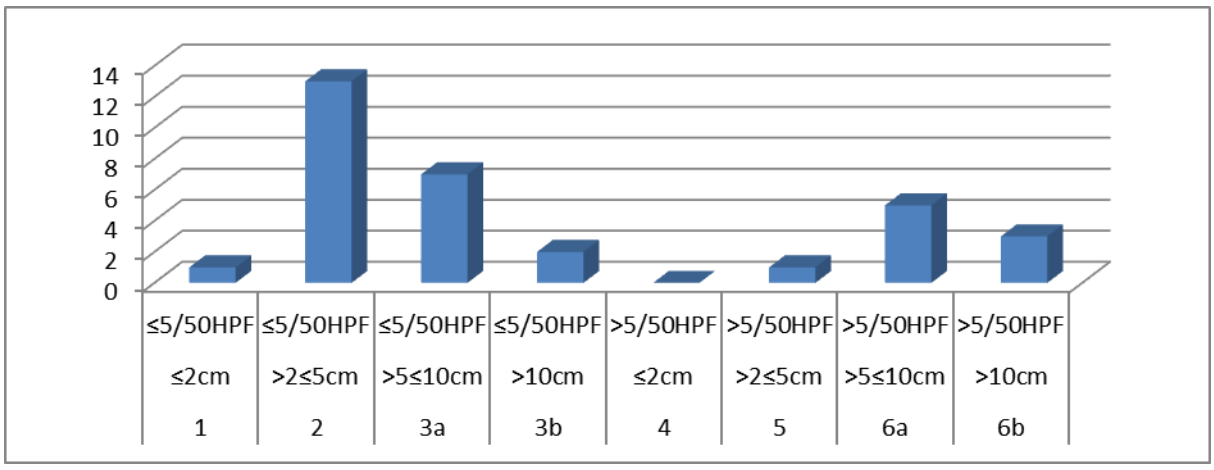
HISTOPATHOLOGICAL TYPES	NO. OF PATIENTS(n=32)
SPINDLE	**24**
EPITHELOID	**5**
MIXED	**3**



Majority of cases showed spindle cell type (75%). 5 cases showed epitheloid histopathology, while 2 were of the mixed variety. Both tumors associated with the mixed subtype were larger and more aggressive. Epitheloid tumors were more commonly seen in the stomach.

STAGEWISE INCIDENCE:

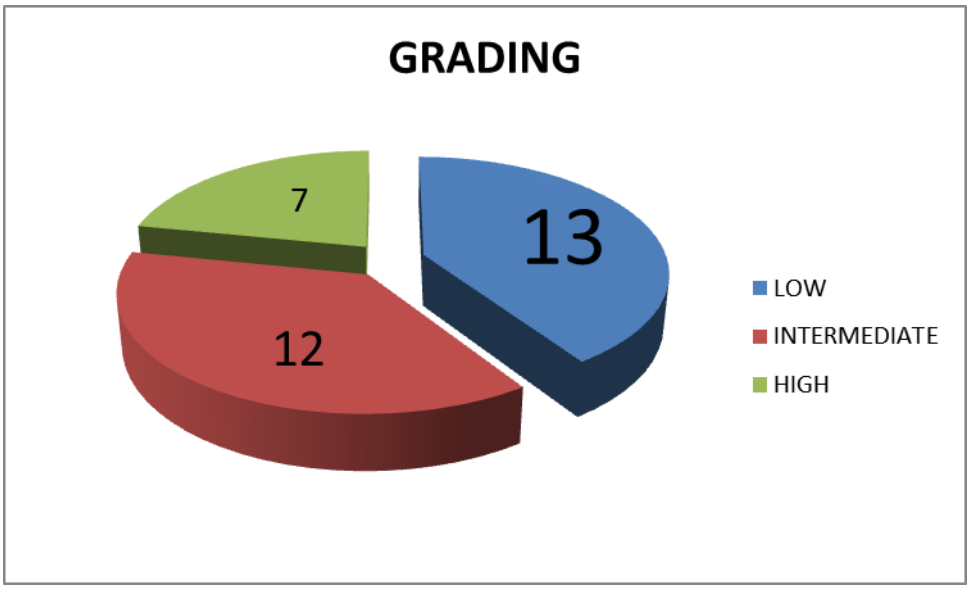
STAGE	SIZE	MITOTIC RATE	NO. OF PATIENTS(n=32)
1	≤2cm	≤5/50HPF	1
2	>2≤5cm	≤5/50HPF	13
3a	>5≤10cm	≤5/50HPF	7
3b	>10cm	≤5/50HPF	2
4	≤2cm	>5/50HPF	0
5	>2≤5cm	>5/50HPF	1
6a	>5≤10cm	>5/50HPF	5
6b	>10cm	>5/50HPF	3



Majority (40%) of patients were found to have prognostic stage 2 disease. However, 25% of all patients were found to have stage 6 disease.

GRADING:

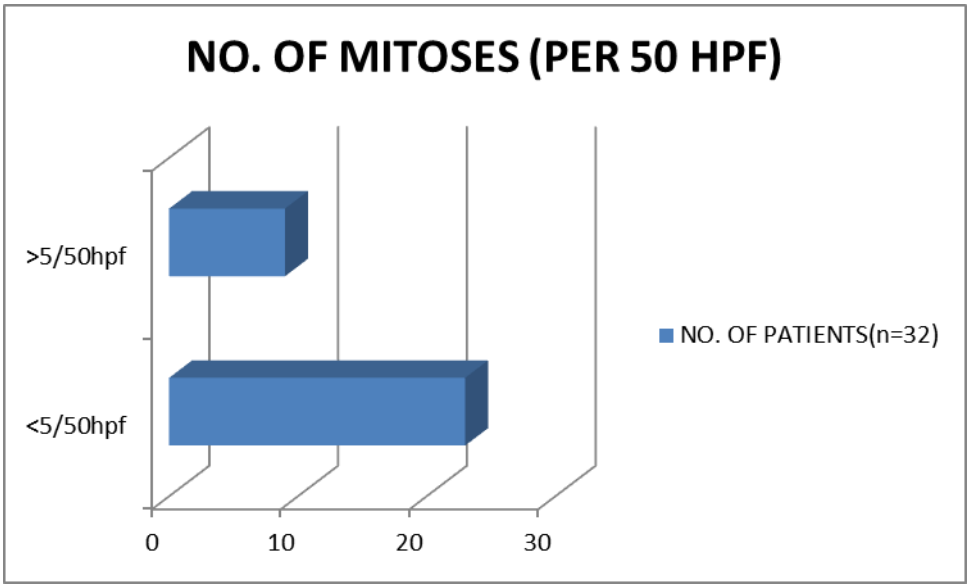
GRADING	NO. OF PATIENTS(n=32)
LOW	**13**
INTERMEDIATE	**12**
HIGH	**7**



Low and intermittent grade tumors were predominantly seen. All three cases of Extraintestinal GIST were found to be of high grade.

NO. OF MITOSES:

NO. OF MITOSES (PER 50 HPF)	NO. OF PATIENTS(n=32)
<5/50hpf	**23**
>5/50hpf	**9**



Most (72%) of the tumors had favourable mitoses (<5/50hpf). All tumors with mixed histopathology had high number of mitoses.

IMMUNOHISTOCHEMISTRY:

All 32 cases of GIST studied were CD117 positive.

DISCUSSION

GIST is a rare and fairly newly baptized neoplasm and both Indian and international data about it is still evolving.

AGE AND SEX DISTRIBUTION:

The majority of patients in our study (65%) were above 50 years of age, with peak incidence between the 60-69 years of age (31%). The median age was 56. This corresponds well with international as well as Indian statistics.[36,72,77,78]

Male patients comprised 59.4% of all GIST cases and female patients the remainder in our study. This is similar to most international and studies. However Indian data suggests male preponderance.[72,78]

PRESENTATION

78% of all patients presented electively in the outpatient department, 22% presented as an acute emergency. When compared to international data, our study shows a slighty higher incidence in emergency presentation.[36] Also, the number of GISTs presenting with unresectable disease was low (15%).The number of cases presenting with metastatic disease (6%) (To the liver) was also lower than most international studies.[36]

CLINICAL FEATURES:

Our study showed that abdominal pain was the predominant symptom, seen in 65% of all patients. GI bleeding was seen only in 10 cases (31%). However, most international studies show GI bleeding to be the most common clinical feature associated with GIST.[2,36] Another Indian study also has shown abdominal pain as the predominant clinical feature in GISTs.[78]

Half of all patients had a palpable abdominal mass at the time of presentation, again a feature not seen in most American studies. Also, only 6% of all cases were incidentally detected. These deviations from international data may be explained by presentation late in the natural history of the disease among lower socio-economic groups (which comprise the majority of the studied population) in India, as is seen in cancers of the stomach and breast.[74,75]

TUMOR LOCATION:

Our study showed almost equal incidence of GIST in the small intestine (43.7%) and stomach (40.6%) . This shows variance from most international studies, which state stomach as the most common organ involved in GIST.[2,13,36] However, our study correlates well with Indian data, which suggests equal incidence between small intestinal and gastric GISTs in the Indian population.[77,78]

9% of patients showed extraintestinal disease, involving the mesentery and omentum. This is higher than most international studies.[2,36] Again, howevr, Indian studies have shown higher incidence of extraintestinal GISTs.[78]

SIZE OF PRIMARY TUMOR:

46% of patients (15) had tumor size in the greatest dimension ≤5cm. 37% patients had primary GIST size between 5-10 cm, while 15% patients had GISTs > 10cm in size. This is on par with other international studies.[2,26,36]

HISTOPATHOLOGY

Most cases showed spindle cell type (75%). 15% of cases showed epitheloid histopathology, while the remaider showed the mixed variety. This data is similar to international statstics.[26,36]

Low and intermittent grade tumors were predominantly seen.

Most (72%) of the tumors had favourable mitoses (<5/50hpf). These findings are similar to international data.

All 32 cases of GIST studied were CD117 positive.

CONCLUSIONS

GIST in Indian population shows slight male preponderance. Also, GI bleeding as a chief presenting complaint, while not infrequent, is superseded by abdominal pain, which was the most common presenting complaint in our study. In most Indian series, including our study, small intestinal and stomach GISTs have similar incidence; also, extraintestinal GISTs appear to be more common in India. The incidence of metastatic disesase and unresectable disease also seems to be lower in the Indian population. Most gross and microscopic histopathological data Indian studies appear to be correlating well with international studies.